

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MASSACHUSETTS

JOHN HANCOCK LIFE INSURANCE
COMPANY, JOHN HANCOCK
VARIABLE LIFE INSURANCE
COMPANY and MANULIFE
INSURANCE COMPANY,

Plaintiffs,

v.

ABBOTT LABORATORIES,

Defendant.

CIVIL ACTION NO. 05-11150-DPW

**ABBOTT'S CORRECTED DEPOSITION DESIGNATIONS AND COUNTER-
DESIGNATIONS FOR AZMI NABULSI**

Defendant Abbott Laboratories ("Abbott") respectfully submits the attached corrected deposition designations and counter-designations for the January 24, 2007 deposition of Azmi Nabulsi, former Venture Head, Oncology Venture, Abbott Laboratories.

Dated: February 22, 2008

Respectfully submitted,

ABBOTT LABORATORIES

By: /s/ Eric J. Lorenzini
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CERTIFICATE OF SERVICE

I hereby certify that this document(s) filed through the ECF system will be sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF) and paper copies will be sent to those indicated as non registered participants on February 22, 2008.

Date: February 22, 2008

/s/ Ozge Guzelsu

Azmi Nabulsi Deposition Designations

Depo Date	Witness	Hancock Designation	Abbott Counter Designation	Abbott Designation	Deposition Exhibit	Plaintiff Exhibit	Defendant Exhibit
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1/24/2007	Nabulsi, Azmi			7:15-9:6			
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1/24/2007	Nabulsi, Azmi			21:3-21:20			
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1/24/2007	Nabulsi, Azmi	90:23-91:5	91:6-91:15		6	I	
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1/24/2007	Nabulsi, Azmi	94:7-94:20	93:20-94:5		6	I	
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1/24/2007	Nabulsi, Azmi			244:18-245:6			
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1/24/2007	Nabulsi, Azmi	264:2-264:23					
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1/24/2007	Nabulsi, Azmi	293:20-294:14					

Color Key to Deposition Designations

 **Designation by Plaintiffs**

 **Counter Designation by Defendants**

 **Designation by Defendants**

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 UNITED STATES DISTRICT COURT
2 FOR THE DISTRICT OF MASSACHUSETTS
3
4
5 JOHN HANCOCK LIFE INSURANCE)
6 COMPANY, JOHN HANCOCK VARIABLE)
7 LIFE INSURANCE COMPANY and)
8 MANULIFE INSURANCE COMPANY)
9 (f/k/a INVESTORS PARTNER)
10 INSURANCE COMPANY),)
11 Plaintiffs,) Civil Action No.
12 -vs-) 05-11150-DPW
13 ABBOTT LABORATORIES,)
14 Defendant.)

15
16 THE VIDEOTAPED DEPOSITION OF
17 AZMI NABULSI
18
19 January 24, 2007
20
21
22
23
24

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 A. Okay.

2 Q. Okay? If you don't understand any of my
3 questions, let me know and I'll try to rephrase
4 them. Okay?

5 A. Okay.

6 Q. If you answer, I'll assume you
7 understood it.

8 A. Okay.

9 Q. Okay.

10 MR. ZWICKER: Greg, we have historically
11 reserved objections except as to form and motions
12 to strike. Is that okay?

13 MR. PHILLIPS: That's fine, yes.

14 MR. ZWICKER: And he can sign -- he need not
15 do so before a notary. Is that okay too?

16 MR. PHILLIPS: That's fine, too.

17 MR. ZWICKER: Okay.

18 BY MR. ZWICKER:

19 Q. Dr. Nabulsi, where are you presently
20 employed?

21 A. Takeda Laboratories. My location in
22 Japan.

23 Q. What do you do for Takeda?

24 A. I am general manager of strategic

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 development department in the development division.

2 Q. What do you do as general manager?

3 A. I'm responsible for the general

4 strategic management of all the development

5 activities at the global level, all the clinical

6 development activities at the global level.

7 Q. Are these for certain kinds of

8 compounds --

9 A. All compounds.

10 Q. -- or all compounds? All compounds.

11 A. All compounds. All the pharmaceutical

12 business.

13 Q. Including oncology?

14 A. Correct.

15 Q. How long have you been at Takeda?

16 A. Since September 2004.

17 Q. Before you were at Takeda, you were at

18 Abbott, right?

19 A. Correct.

20 Q. What was your last job at Abbott?

21 A. I was vice president of global medical

22 affairs.

23 Q. How long did you hold that position?

24 A. Two years.

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 Q. From when to when?

2 A. 2002 to 2004, till I left.

3 Q. What did you do as vice president for
4 global medical affairs?

5 A. I was responsible of all the medical
6 departments outside the US. I was responsible for
7 all the clinical, global clinical operation
8 activities, professional development and health
9 economics.

10 Q. Did your responsibilities include all
11 compounds under development by Abbott or just some?

12 A. All compounds. At the medical affairs
13 level.

14 Q. What does that mean?

15 A. It means I was not responsible for the
16 development to get these compounds approved and on
17 the market, but I was responsible to support them
18 beyond the approval stage.

19 Q. So, once the FDA approved them, you
20 assisted in the commercialization process. Is that
21 fair?

22 A. I assisted in additional research to
23 support the products while they're on the market.

24 Q. Okay. Why did you leave Abbott?

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 A. Why?

2 Q. Yes.

3 A. I left Abbott because I looked for other
4 opportunities after being there ten years.

5 Q. You weren't asked to leave, were you?

6 A. No.

7 Q. Before you were vice president, from
8 2002 to 2004, what was the previous job you had at
9 Abbott?

10 A. I was the venture head of the oncology
11 venture.

12 Q. From when to when?

13 A. 1999 to 2002.

14 Q. What were your responsibilities as
15 venture head for oncology?

16 A. To bring all oncology compounds from
17 research into development and take them through the
18 development phases towards approval.

19 Q. Who did you report to?

20 A. Perry Nisen.

21 Q. Over the entire period 1999 to 2002?

22 A. Initially when we started I was
23 reporting to Louise Dubay.

24 Q. That was when?

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 A. That was '98, '99, as the oncology part
2 of my work.

3 Q. And beginning in 1999 you began
4 reporting to Perry Nisen?

5 A. Sometime in '99. I don't recall what --
6 what months exactly.

7 Q. What was Nisen's title at Abbott when
8 you reported to him?

9 A. When I reported to him he was vice
10 president of oncology development.

11 Q. What's the difference between vice
12 president of oncology and venture head for
13 oncology?

14 A. Vice president was a more strategic job.
15 So, he was at a level what we called at the time
16 therapeutic area committee. So, for instance, he
17 is -- he is part of that committee, which
18 coordinate all the strategic future for the
19 oncology side of the Abbott while I was primarily
20 responsible for the development, clinical
21 development, of the compounds.

22 Q. Fair to say that you're more on the
23 ground with the compounds than he is?

24 A. That's right.

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 Q. What was your job at Abbott before
2 venture head during '99 to 2002?

3 A. I was the medical director for the
4 immunology and transplant venture.

5 Q. What were your responsibilities?

6 A. Development of the immunology compounds,
7 particular at the time asthma compound, allergic
8 rhinitis and a few other particular. Transplants
9 as well.

10 Q. Over what dates did you hold that
11 position?

12 A. That one, late '96 to '99.

13 Q. Your position as medical director had
14 nothing to do with oncology, is that right?

15 A. That's right.

16 Q. Before you were medical director what
17 was your previous job at Abbott?

18 A. I was associate medical director in the
19 health economics and outcomes research group.

20 Q. From when to when?

21 A. '94 to '96.

22 Q. That was your first job at Abbott,
23 right?

24 A. Sure.

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 Q. Prior to working for Abbott, who did you
2 work for?

3 A. Burroughs Wellcome in North Carolina.

4 Q. Say that again.

5 A. Burroughs Wellcome.

6 Q. Spell it.

7 A. B-u-r-r-o-u-g-h-s, Wellcome with two Ls.

8 Q. And that was in Lake Forest, Illinois?

9 A. No, no. That was in North Carolina.
10 Research Triangle Park.

11 Q. How long were you there?

12 A. Two years.

13 Q. '92 to '94?

14 A. That's right.

15 Q. What did you do?

16 A. I was an epidemiologist.

17 Q. Before Burroughs, did you have other
18 jobs in which you were involved in oncology?

19 A. No.

20 Q. Can you briefly describe for me your
21 educational background beginning with college?

22 A. I went to medical school in Egypt and
23 then moved -- after medical school, moved to
24 University of Minnesota where I did Master's of

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 public health, epidemiology, and I worked there as
2 well.

3 Q. When did you graduate from medical
4 school?

5 A. '84.

6 Q. And when did you earn your MPH from the
7 University of Minnesota?

8 A. 1990.

9 Q. I want to focus on the period where you
10 were venture head for oncology in '99 to 2002.
11 Okay?

12 A. Okay.

13 Q. During that period you said you reported
14 to Perry Nisen, right?

15 A. Correct.

16 Q. Who did Nisen report to?

17 A. John Leonard.

18 Q. Did Leonard report to Dr. Leiden?

19 A. Correct.

20 Q. How did you prepare for your testimony
21 today?

22 A. I met with the counsel yesterday.

23 Q. Mr. Phillips?

24 A. Yes.

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 the document. It's the -- describing the product,
2 a document that described the product to
3 John Hancock. I forgot the name of the document.
4 I saw a couple presentations as well that were
5 internal presentations.

6 Q. Okay. Did you have an opportunity to
7 meet with Mr. Phillips this morning as well?

8 A. Just we drove together. I drove him in.
9 But it wasn't a meeting.

10 Q. Okay. And this morning, did he show you
11 any additional documents?

12 A. No.

13 Q. I take it that your job at Abbott when
14 you first became involved with the development of
15 ABT-518 was venture head for oncology, is that
16 right?

17 A. It may not have been venture head title
18 at the very first involvement, but quickly I became
19 the venture head.

20 Q. As venture head for oncology, and I'm
21 asking you specifically about 518 now.

22 A. Okay.

23 Q. Okay? What were your responsibilities
24 for 518?

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 A. To take that product from research, put
2 the development plan, get it approved, get the
3 product into the clinical development and move it
4 ultimately forward towards submission and approval.

5 Q. You were supervising the development of
6 other oncology programs at the same time, correct?

7 A. Correct.

8 Q. How many others?

9 A. There were probably six or so.

10 Q. ABT-518 is known as an MMPI, right?

11 A. Correct.

12 Q. 518 was the only MMPI you were
13 responsible for, right?

14 A. No.

15 Q. There was --

16 A. At the time was yes, but there were --
17 there were more than one MMPI that we were working
18 on to bring forward. But 518 became the candidate
19 to take forward.

20 Q. At one point you had responsibility for
21 970?

22 A. No 970.

23 Q. ABT-970. 770?

24 A. Yes.

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 Q. And eventually 518 displaced 9 -- 770 as
2 the premier candidate?

3 A. Correct.

4 Q. At that point the sole MMPI drug that
5 you were responsible for was 518?

6 A. Correct.

7 Q. What's a project team?

8 A. It's a group of individuals who -- who
9 have the skills to bring a project forward. They
10 come from within clinical, within preclinical
11 functions. They come from other functional areas
12 like statistics, data management and so on.

13 So, as a group, they have the
14 appropriate skill to support a product totally.

15 Q. There was a project team for 518,
16 correct?

17 A. Correct.

18 Q. Were you ostensibly in charge of the
19 project team?

20 A. Yes.

21 MR. PHILLIPS: Objection to form.

22 Dr. Nabulsi, just give me a moment to
23 interpose an objection if I feel it's necessary.

24 Thank you.

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 BY MR. ZWICKER:

2 Q. Did you supervise the activities of the
3 project team?

4 A. Yes.

5 Q. All project team members reported to
6 you?

7 MR. PHILLIPS: Objection to the form.

8 BY MR. ZWICKER:

9 Q. In the -- let me see if I can address
10 the objection.

11 In the period 2000 to 2001 did all
12 project team members for 518 report to you?

13 A. No.

14 Q. Who didn't?

15 A. Members from other functions did not
16 report to me. If there is a member -- when there
17 is a member from research, they don't report to me
18 directly. They report to research. A member
19 from -- from toxicology would report to toxicology.
20 They are engaged in the project. I manage the
21 project activity, but they don't report to me as
22 a -- as the direct manager.

23 Q. Fair to say, though, that you were
24 supervising all activities relating to the

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

- 1 development of 518 in 2000 and 2001, correct?
- 2 A. Correct.
- 3 Q. The development activities for 518 in
- 4 the 2000 and 2001 period included the following:
- 5 Preclinical work, right?
- 6 A. Can you repeat the question?
- 7 Q. Yeah. I want to get the sense of all
- 8 the development activities relating to 518 in the
- 9 2000/2001 period. Got it?
- 10 A. Yes.
- 11 Q. Those activities included toxicology?
- 12 A. Yes.
- 13 Q. Clinical work?
- 14 A. Yes.
- 15 Q. Regulatory work?
- 16 A. Yes.
- 17 Q. Commercialization?
- 18 A. No. Commercialization, depend how you
- 19 define commercialization. The product was still
- 20 very early stage of development.
- 21 Q. Who is Lise Loberg?
- 22 A. New product planning.
- 23 Q. Were you -- was Lise Loberg part of the
- 24 518 project team?

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 A. Yes.

2 Q. You were aware of her responsibilities?

3 A. Yes.

4 Q. And were part of her responsibilities to

5 position the product for eventual

6 commercialization?

7 MR. PHILLIPS: Objection to form.

8 BY THE WITNESS:

9 A. Lise was responsible to define the

10 future direction of the marketing of the product.

11 BY MR. ZWICKER:

12 Q. What's PK?

13 A. Pharmacokinetics.

14 Q. What is that?

15 A. Looking at the absorption and

16 distribution of the chemical in the body once it's

17 absorbed.

18 Q. PK was part of the development

19 activities for 518, right?

20 A. Correct.

21 Q. And you supervised that aspect too,

22 correct?

23 A. Correct.

24 Q. Were there other aspects of the 518

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 development process that you supervised that I
2 haven't mentioned?

3 A. No.

4 Q. In the period 2000 to 2001 -- and,
5 Dr. Nabulsi, if at a point I neglect to identify
6 the period of my question.

7 A. Um-hmm.

8 Q. Assume it's 2000 to 2001. Okay?

9 A. Okay.

10 Q. In the period 2000/2001 what documents
11 were created by the project team in connection with
12 the development of 518?

13 MR. PHILLIPS: Object to the form.

14 BY THE WITNESS:

15 A. It's very broad.

16 BY MR. ZWICKER:

17 Q. Okay. Are you familiar with a monthly
18 highlight report?

19 A. Yes.

20 Q. Was a monthly highlight report created
21 by the project team?

22 A. Yes.

23 Q. Who created it?

24 A. I don't recall the name, but typically

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1 they are created by the -- either associate

2 director or by the senior project manager.

3 Q. Who was the associate director in

4 2000/2001?

5 A. Susan Glad I believe it was.

6 Q. Spell it.

7 A. Susan Glad Anderson.

8 Q. And who was the senior project manager?

9 A. Diane D'Amico I believe.

10 Q. Did Diane D'Amico's responsibilities for

11 518 include more than just overseeing the clinical

12 trial?

13 A. No.

14 Q. That's all she did?

15 A. That's right.

16 Q. Other than monthly highlight reports,

17 what documents were created by the project team?

18 A. Again, this is very broad because the

19 project team is a wide range of -- big team. Can

20 you be more specific?

21 Q. Are you familiar with the MMPI working

22 group?

23 A. It is -- I don't recall the term

24 "working group."

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1 A. Yes.

2 Q. At what point were those reports

3 created?

4 Let me give you an example. Take a

5 report that's dated February 2001. Would that

6 report be created during the first few days of

7 March or during February?

8 MR. PHILLIPS: Object to the form.

9 BY THE WITNESS:

10 A. Actually I don't understand the

11 question.

12 BY MR. ZWICKER:

13 Q. Okay. I'm going to come back to it.

14 As part of your responsibility as

15 venture head for oncology, did you attend seminars

16 and conferences that related to the development of

17 518?

18 A. Internal or external?

19 Q. Both.

20 A. Yes.

21 Q. What external conferences did you

22 attend?

23 A. Advisory committee meetings,

24 investigator meetings.

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1 Q. Investigator meetings are with the
2 persons who are running the clinical sites for
3 clinical programs?

4 A. Yes.

5 Q. Are you familiar with an entity called
6 ASCO?

7 A. Yes.

8 Q. What does that stand for?

9 A. American Society of Clinical Oncology.

10 Q. In 2000/2001 did you attend ASCO
11 meetings?

12 A. I don't recall specifically.

13 Q. Did you personally in 2000/2001 view --
14 strike that.

15 What happened at ASCO meetings?

16 MR. PHILLIPS: Object to the form.

17 BY MR. ZWICKER:

18 Q. Are you aware of what happened at ASCO
19 meetings?

20 A. In general --

21 Q. Yes.

22 A. -- ASCO meetings?

23 Q. Yes.

24 A. People -- oncology investigators and

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1 researchers present data from all over the world.

2 Q. With respect to what?

3 A. To new findings, new data on clinical

4 trials, report clinical trial results, orally or

5 posters, written presentations.

6 Q. What's a poster?

7 A. It's a poster which is clinical or

8 preclinical data that's presented on a sheet of

9 paper, 3 by 6, describing the research and its

10 outcome that's put on a board and people can come

11 in, read the results, talk to the -- talk to the

12 researcher who is standing by the -- by the poster,

13 ask him about the research and the outcome of that

14 research.

15 Q. Was Abbott aware of some of the

16 information presented at ASCO before the ASCO

17 conference?

18 MR. PHILLIPS: Object to the form.

19 BY THE WITNESS:

20 A. I don't know. Typically, though, you --

21 these results are not shared except on the day of

22 the presentation. There is a book that ASCO

23 releases a few days before or maybe a couple weeks

24 before the meeting that describes some of the

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1 results. But you don't see the details of the

2 results till you attend the meeting.

3 MR. PHILLIPS: Excuse me, counsel.

4 Mr. Videographer, is Mr. --

5 Dr. Nabulsi's voice sometimes gets very low. Is

6 he -- is the video picking it up?

7 THE VIDEOGRAPHER: Yes.

8 MR. PHILLIPS: Thank you.

9 BY MR. ZWICKER:

10 Q. Fair to say, sir, that Abbott became

11 aware of information relating to 518 separate and

12 apart from ASCO presentations. True?

13 MR. PHILLIPS: Objection to the form.

14 BY THE WITNESS:

15 A. I don't understand. Repeat the

16 question.

17 BY MR. ZWICKER:

18 Q. ASCO wasn't the only way that Abbott

19 became aware of what other companies were doing

20 with MMPI compounds, correct?

21 A. Correct.

22 Q. There was publicly available

23 information, wasn't there?

24 A. Correct.

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1 appropriate fashion compared -- relative to
2 everything else in the portfolio.

3 Q. In 2000/2001, to whom was the portfolio
4 review for oncology made?

5 Let me ask a different question.

6 To whom at the portfolio reviews, to
7 whom did you report?

8 MR. PHILLIPS: Object to the form.

9 BY THE WITNESS:

10 A. I did not report directly in the
11 portfolio review. That was Perry's job, to report
12 directly. But the audiences were top management in
13 the company.

14 BY MR. ZWICKER:

15 Q. Dr. Leiden?

16 A. Correct.

17 Q. Dr. Leonard?

18 A. Correct.

19 Q. Bill Dempsey?

20 A. I don't recall if Bill Dempsey was in
21 that meeting at the time.

22 Q. Do you know what a go/no go decision is?

23 A. Yes.

24 Q. Were go/no go decisions made at

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 Q. Yeah. What was the role of the PEC?

2 A. It's the ultimate decision-making body

3 in the company, pharmaceutical side of the company.

4 Q. In 2000/2001 was Dr. Leiden ultimately

5 in charge of making go/no go decisions for

6 compounds under development?

7 MR. PHILLIPS: Objection to the form.

8 BY THE WITNESS:

9 A. If he was -- if he was heading the PEC

10 at the time. I don't recall. I believe he was.

11 BY MR. ZWICKER:

12 Q. The person who headed the PEC had

13 ultimate responsibility to make go/no go decisions

14 for compounds, is that right?

15 MR. PHILLIPS: Object to the form.

16 BY THE WITNESS:

17 A. Can you repeat?

18 BY MR. ZWICKER:

19 Q. Yeah. Whoever headed the PEC in

20 2000/2001 was ultimately responsible for making

21 go/no go decisions regarding the development of

22 compounds. True?

23 MR. PHILLIPS: Object to the form.

24 BY THE WITNESS:

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1 A. Yes.

2 (WHEREUPON, a certain document was

3 marked Nabulsi Deposition Exhibit

4 No. 1, for identification, as of

5 01-24-2007.)

6 BY MR. ZWICKER:

7 Q. Dr. Nabulsi, the Reporter has put before

8 you what has been marked as Nabulsi Exhibit No. 1.

9 It's titled "Matrix Metalloproteinase Inhibitors

10 Project, Discovery Development Candidate Meeting,

11 March 9, 2000."

12 Do you see that?

13 A. Yes.

14 Q. Do you recognize this document?

15 A. Not this particular one, no.

16 Q. Do you recognize documents like it?

17 A. Yes.

18 Q. What is it?

19 A. This is the format that the research

20 group used to present their portfolio when they

21 present the research candidates describing the

22 product, their activity, the profile and their

23 recommendation for moving forward or not.

24 Q. As of March 9, 2000, who was the

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 research group?

2 MR. PHILLIPS: Who was -- object to the form.

3 BY THE WITNESS:

4 A. This is very broad question.

5 BY MR. ZWICKER:

6 Q. Do you know as of March 9, 2000, who

7 would have been responsible for creating this

8 document?

9 A. Not specifically, no.

10 Q. Would you have reviewed this document in

11 the course of your responsibilities as venture

12 head?

13 A. Not to approve it for -- no. I would

14 have -- if I reviewed it, I would have reviewed it

15 prior to attending the meeting but not to approve

16 it to go forward. So, it was -- such document was

17 not my responsibility.

18 Q. Your responsibility to create?

19 A. Or approve as correct. That is research

20 responsibility.

21 Q. What is the purpose of the development,

22 the discovery development candidate meeting?

23 A. That's the research -- research team

24 bring forward their candidate which they recommend

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1 table.

2 BY MR. ZWICKER:

3 Q. Do you recognize those four compounds?

4 A. I know of them, yes.

5 Q. What are they?

6 A. They're MMPI inhibitors from other

7 companies, competitor MPPI inhibitors.

8 Q. Competitors?

9 A. To 518.

10 Q. Is it fair to say that in March 2000

11 Abbott was tracking the development status of these

12 four MMPI competitors?

13 A. Yes.

14 Q. Why?

15 A. This is a usual practice in any -- for

16 any compound, to look at what's going on in the

17 field overall, what's going on with the

18 competition, so you gather intelligence so you can

19 develop a competitive compound.

20 Q. There were more than four MMPI

21 competitors under development in March 2000,

22 weren't there?

23 A. I don't recall how many.

24 Q. In March of 2000, did Abbott believe

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 that these four competitors were the most important
2 in determining the success of ABT-518?

3 MR. PHILLIPS: Object to the form.

4 BY THE WITNESS:

5 A. I can't answer specifically.

6 BY MR. ZWICKER:

7 Q. Certainly you would agree with me that
8 Abbott deemed these four competitors to be
9 important enough to track their development status.
10 True?

11 A. Important enough to track.

12 Q. Sitting here today, can you think of any
13 other development candidates, any other competitors
14 whose development Abbott was tracking in 2000/2001?

15 A. No.

16 Q. In March 2000 how did Abbott keep
17 abreast of developments relating to these four
18 competitor MMPs?

19 A. Primarily scientific meetings and
20 publications.

21 Q. What kind of meetings?

22 A. ASCO, AACR, others similar to those.

23 Q. What's AACR?

24 A. I believe American Association of Cancer

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 Q. Did Abbott keep abreast of materials in
2 publicly available databases?

3 A. Can you please repeat?

4 Q. Did Abbott check publicly available
5 databases for the status of its MMPI competitors?

6 A. Yes.

7 Q. Who did that? Whose job was it?

8 A. That would have been the research
9 project leader's job, the new product planning job
10 and --

11 Q. Who was the research project leader?

12 A. At the time I believe Steve Davidsen.

13 Q. You said that Abbott purchased publicly
14 available reports as well, didn't you?

15 A. That's right.

16 Q. And, in fact, Abbott did purchase those
17 reports for MMPI competitors, right?

18 A. I don't recall specifically, but that
19 was a practice that was done.

20 Q. Are you familiar with the Institute For
21 Scientific Information?

22 A. No.

23 Q. Are you familiar with NIH databases?

24 A. NI -- I don't know what you mean by

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1 that. There are a lot of databases.

2 Q. National Institute of Health database.

3 A. Which specific database?

4 Q. Was there a database put out by the NIH

5 that allowed Abbott to check the development status

6 of the MMPI competitors?

7 A. I -- I don't know about that.

8 Q. Do you know what Tox Line is?

9 A. Vaguely, very vaguely.

10 Q. In the 2000/2001 time period did you

11 personally believe that Abbott adequately kept

12 abreast of the development status of these four

13 MMPI competitors, the ones listed at Exhibit 1?

14 A. Yes.

15 Q. Take a look again, Dr. Nabulsi, at

16 page 2. The first program that's listed in the

17 chart is marimastat. Do you see that?

18 A. Um-hmm.

19 Q. By the way, did I pronounce that

20 correctly?

21 A. Marimastat, yeah.

22 Q. Marimastat, m-a-r-i-m-a-s-t-a-t.

23 A. And it's pronounced marimastat.

24 Q. You would agree with me, wouldn't you,

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1 that in March of 2000 Abbott knew that marimastat
2 showed joint toxicity issues in testing. True?

3 A. Yes.

4 Q. Abbott also knew that in March 2000,
5 marimastat was in Phase III clinical trials, right?

6 A. Yes.

7 Q. Turn to page 28 of the document. Look
8 at the slide titled "Status of Competition,
9 Agouron, Bristol-Myers Squibb."

10 Do you see that?

11 A. Yes.

12 Q. I'm sorry. I directed you to the wrong
13 page. It's actually going to be page 28.

14 MR. PHILLIPS: I thought that's what you did.

15 THE WITNESS: 28.

16 MR. ZWICKER: Oh, I did -- I did.

17 BY MR. ZWICKER:

18 Q. My apologies. Page 25. Same top slide.

19 You would agree with me that in
20 March 2000, Abbott also knew that marimastat had
21 not shown efficacy in pancreatic cancer, correct?

22 MR. PHILLIPS: Objection to the form.

23 BY THE WITNESS:

24 A. I don't recall. I need to read the

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 slide to recall.

2 BY MR. ZWICKER:

3 Q. Go ahead. See if it refreshes your
4 recollection.

5 A. So, based on this slide in
6 non-resectable pancreatic cancer, marimastat did
7 not show activity.

8 Q. And to your recollection Abbott viewed
9 that as a negative development for the prospects
10 for 518. True?

11 MR. PHILLIPS: Object to the form.

12 BY THE WITNESS:

13 A. To answer your question as stated, I
14 would say no.

15 BY MR. ZWICKER:

16 Q. Why?

17 A. Because that was negative for
18 marimastat. For 518, there is nothing to say
19 anything specifically about 518. That's -- that's
20 only one other class member did not show efficacy.
21 But 518 itself, we don't know yet. It will cause
22 us to pause and think how this affects 518.

23 Q. You would agree with me that the results
24 from the four compounds that Abbott is tracking has

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1 some impact on Abbott's thinking about whether to
2 continue development of 518. True?

3 MR. PHILLIPS: Object to the form.

4 BY THE WITNESS:

5 A. Can you restate that?

6 BY MR. ZWICKER:

7 Q. Yeah. You would agree with me that the
8 developmental status of the four MMPI competitors
9 is relevant to Abbott's consideration about whether
10 to continue development of 518, right?

11 MR. PHILLIPS: Object to the form.

12 BY THE WITNESS:

13 A. It created concern about 518.

14 BY MR. ZWICKER:

15 Q. It's -- the development status of the
16 competitors is something Abbott considered. True?

17 A. Considered, yes.

18 Q. And to the extent that a 518 competitor
19 released bad data regarding efficacy, that would be
20 something Abbott considered. True?

21 A. Correct.

22 Q. Turn to page -- return to page 2.

23 The second compound listed is

24 prinomastat. Do you see that?

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1 A. Yes.

2 Q. In March 2000 Abbott knew that

3 prinomastat was in Phase III clinical compounds,

4 right?

5 MR. PHILLIPS: Objection to the form.

6 BY THE WITNESS:

7 A. Could you repeat, please.

8 BY MR. ZWICKER:

9 Q. Yes. In March 2000 Abbott knew that

10 prinomastat was in Phase III clinical trials.

11 True?

12 A. Based on this slide, yes.

13 Q. And to your recollection as well?

14 A. Yes.

15 Q. Abbott also knew in March 2000 that

16 prinomastat was showing joint toxicity in clinical

17 trials. True?

18 A. Yes.

19 Q. Sir, do you know where the data in the

20 slide on page 2 came from regarding the MMPI

21 competitors?

22 MR. PHILLIPS: Object to the form.

23 BY THE WITNESS:

24 A. You're referring to a person or a

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 source?

2 BY MR. ZWICKER:

3 Q. Source.

4 A. No.

5 Q. Whose job was it to compile the data
6 that was in the slide on page 2?

7 A. Would have been Steve Davidsen.

8 Q. Turn again to page 28 and look, if you
9 will, at the portion of the slide that relates to
10 prinomastat.

11 Sir, it's fair to say in your
12 recollection that as of March 2000 Abbott was
13 monitoring the Phase III results for testing of
14 prinomastat on non-small cell lung cancer and
15 prostate cancer. True?

16 A. Monitoring the progress of the
17 Phase III.

18 Q. And the results of those Phase III
19 trials were important to Abbott. Fair?

20 A. Yes.

21 Q. Why is that?

22 A. Because it's information that will teach
23 us about the class, will teach us how to better
24 develop 518.

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1 Q. And is it also a way of determining or
2 drawing some conclusions regarding whether 518 will
3 be efficacious against cancers?

4 A. No.

5 Q. Why?

6 A. Because, again, the tested product in
7 Phase III is prinomastat, not 518.

8 Q. But you would agree with me, sir,
9 wouldn't you, that if the Phase III studies for
10 prinomastat reflect no efficacy for the compound,
11 that that would not be positive data for the
12 development of 518, right?

13 A. That will increase the risk for 518.

14 Q. Turn back to page 2.

15 Dr. Nabulsi, you would agree with me,
16 wouldn't you, that for Abbott the two most
17 important compounds under development as far as 518
18 were concerned were prinomastat and marimastat,
19 correct?

20 MR. PHILLIPS: Objection to the form.

21 BY THE WITNESS:

22 A. No.

23 BY MR. ZWICKER:

24 Q. They were the only two compounds in

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 Phase III development in March 2000, right?

2 MR. PHILLIPS: Object to the form.

3 BY THE WITNESS:

4 A. I cannot answer specifically. I don't

5 recall if there were others.

6 BY MR. ZWICKER:

7 Q. Of the four -- fair.

8 Of the four compounds listed on the

9 chart on page 2, only two of them are in Phase III

10 development, right?

11 A. According to this slide, yes. However,

12 if you look at Bayer, it had Phase III that was

13 scratched and say withdrawn. So, I don't recall

14 the status of Bayer compound.

15 Q. Well, let me ask you: As of March 2000,

16 looking at the slide, isn't it a fact that Bayer

17 had terminated its Phase III development of its

18 compound?

19 MR. PHILLIPS: Object to the form.

20 BY THE WITNESS:

21 A. According to this slide, withdrawn. I

22 recall that Bayer eventually did stop development

23 of their compound. I don't recall the exact

24 timing. But according to this slide, must have

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 been done by the March time frame. 2000 time
2 frame.

3 BY MR. ZWICKER:

4 Q. And withdrawn means that development had
5 been discontinued, right?

6 MR. PHILLIPS: Object to the form.

7 BY MR. ZWICKER:

8 Q. To your knowledge.

9 A. Withdrawn would -- could have meant
10 stopping development, yes.

11 Q. Do you know?

12 A. Not 100 percent.

13 Q. Are you relatively confident?

14 A. That's what I would conclude this means.
15 Based on what I know about Bayer, that stopped too.

16 Q. Turn to page 27 and take a look at the
17 slide that reflects the status of the Bayer drug,
18 which is tanomastat.

19 A. Um-hmm.

20 Q. And look at the -- look at the entire
21 slide. Let me know when you're done.

22 A. Okay.

23 Q. Okay. You see the portion that says at
24 the bottom of the slide, "BAY 12-9566 withdrawn

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1 from all trials as 'precautionary measure.'"

2 Do you see that?

3 A. Yes.

4 Q. You would agree, then, that the Bayer
5 drug was -- development of the Bayer drug was
6 essentially terminated as of March 2000, right?

7 MR. PHILLIPS: Object to the form.

8 BY THE WITNESS:

9 A. Can you rephrase the last part?

10 BY MR. ZWICKER:

11 Q. Sure. You would agree based on your
12 review of the slide that the Bayer drug was
13 withdrawn from development as of March 2000?

14 MR. PHILLIPS: Object to the form.

15 BY THE WITNESS:

16 A. According to this, it's withdrawn from
17 all trials. I cannot say if they stopped all
18 development because they had arthritis as well they
19 were looking into.

20 BY MR. ZWICKER:

21 Q. Okay. You would also agree with me that
22 the withdrawal of the Bayer drug from all trials is
23 not a positive factor for the development of 518?

24 MR. PHILLIPS: Object to the form.

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1 BY THE WITNESS:

2 A. Increases concern level for 518.

3 BY MR. ZWICKER:

4 Q. Turn back to page 2. The last of the
5 four drugs listed in the chart is BMS 275291, which
6 from here on I'm just going to refer to as the BMS
7 drug. Okay?

8 A. Okay.

9 Q. As of March 2000 Abbott knows that the
10 BMS drug is in Phase II trials, correct?

11 A. Yes.

12 Q. Abbott knows that the BMS drug is
13 showing joint toxicity, right?

14 MR. PHILLIPS: Object to the form.

15 BY THE WITNESS:

16 A. According to this slide, yes.

17 BY MR. ZWICKER:

18 Q. And according to your recollection? Do
19 you remember?

20 A. Yes.

21 Q. As of March 2000 Abbott didn't have data
22 regarding the efficacy of the BMS drug on any kinds
23 of cancers, did it?

24 A. I don't recall.

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1 MR. PHILLIPS: Object to the form.

2 BY THE WITNESS:

3 A. I don't recall the other compounds that
4 was tracked, but we tracked all compounds in
5 development. I don't recall the number of those
6 compounds.

7 BY MR. ZWICKER:

8 Q. But none of those compounds are listed
9 on page 5 of Exhibit 2, right?

10 A. I only see four compounds on page 5.

11 Q. Sir, in your own mind, were the
12 marimastat and the prinomastat drugs the most
13 important for you in assessing the likelihood of
14 success for 518?

15 A. Phase III compounds would have been very
16 important.

17 Q. More important than other drugs that
18 weren't in Phase III?

19 MR. PHILLIPS: Object to the form.

20 BY THE WITNESS:

21 A. Would be more informing than other
22 drugs.

23 BY MR. ZWICKER:

24 Q. And, sir, you would agree with me that

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 about that.

2 MR. ZWICKER: That's okay. Here's the next

3 exhibit.

4 (WHEREUPON, a certain document was

5 marked Nabulsi Deposition Exhibit

6 No. 3, for identification, as of

7 01-24-2007.)

8 MR. ZWICKER: The record should reflect that

9 before the witness is Nabulsi Exhibit No. 3, which

10 is entitled "ABT-518 Transition Strategy (MMPI)

11 August 2000."

12 BY MR. ZWICKER:

13 Q. Do you see that, Dr. Nabulsi?

14 A. Yes.

15 Q. Do you recognize this document?

16 A. Yes.

17 Q. Did you help prepare it?

18 A. Yes.

19 Q. What portions of it did you prepare?

20 A. This would have been generated by my

21 team. So, I would have reviewed it and approved

22 it.

23 Q. And when you say review it, you reviewed

24 it for accuracy. Is that true?

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1 A. That's right.

2 Q. What was the purpose of this transition

3 strategy document? What was it used for?

4 A. This is to describe our plan to bring a

5 candidate from research into development stage;

6 what we planned to do, how we are going to plan to

7 take it forward, through the development phases,

8 how much it's going to cost.

9 However, we focus our -- our efforts at

10 the time in the transition document about early

11 stages of development to try to describe or to try

12 to unveil the characteristics of the compounds and

13 assure its -- and able to find out its

14 appropriateness for further development.

15 Q. The document is dated August 2000.

16 A. Yes.

17 Q. Was it actually completed in September?

18 A. I don't recall.

19 Q. I'd like you to focus on pages 3 and 4

20 of Nabulsi Exhibit 3, which is the portion of the

21 document that relates to competitor data. You can

22 read that if you can.

23 A. Okay.

24 Q. Okay. Now, Dr. Nabulsi, isn't it a fact

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1 that on August 4, 2000, Abbott learned that Pfizer,
2 which was developing prinomastat, discontinued
3 Phase III trials for certain advanced lung cancers
4 and in certain advanced prostate cancers?

5 A. Yes.

6 Q. Do you recall that, sitting here today?

7 A. This refreshes my memory. I don't
8 recall it vividly.

9 Q. But you recall it having read that?

10 A. Yeah. Yes.

11 Q. Now, certainly Abbott didn't view the
12 termination of Phase III trials for these cancer
13 indications as good news for the development of
14 518, did it?

15 A. Depends how you look at it, because when
16 you look at the competitive environment, so you
17 look for the results of the competition in two
18 ways. One to learn how to develop your drug
19 better.

20 So, failures of competition could teach
21 you -- could be an opportunity, too, because they
22 teach you how to do your drug better, but also you
23 have less competition if you have a better drug
24 that can maneuver through this -- this field.

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1 So, for instance, 518 was not the first
2 MMPI by any means, right? So if you have the later
3 stage MMPI drop out of the way, then the
4 marketplace become more attractive for 518.
5 At the same time, you have to look at
6 the reasons why the other compounds dropped and see
7 if your drug is devoid of those reasons and can 518
8 succeed and become a drug. So, you have to look at
9 the two sides of the equation.

10 Q. Fair to say that Abbott was very
11 concerned about whether MMPIs actually inhibited
12 certain kinds of proteins, correct?

13 MR. PHILLIPS: Object to the form.

14 BY THE WITNESS:

15 A. I cannot answer that because I don't
16 know. Frankly, I don't know what the question
17 means.

18 BY MR. ZWICKER:

19 Q. My question?

20 A. Yeah.

21 Q. Abbott was interested in seeing that its
22 competitors were demonstrating efficacy in
23 Phase III trials. True?

24 MR. PHILLIPS: Object to the form.

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1 BY THE WITNESS:

2 A. Would be interested to see what the
3 competition is doing for two reasons. One, if they
4 show efficacy, then we need to know how would our
5 drug compare to those. Do we have a potentially
6 better drug or not.

7 BY MR. ZWICKER:

8 Q. All things being --

9 MR. PHILLIPS: I'm sorry. I'm not sure
10 Dr. Nabulsi was finished.

11 BY MR. ZWICKER:

12 Q. I'm sorry. I didn't mean to interrupt
13 you. Go right ahead.

14 A. On the other hand, if they don't show
15 efficacy, we need to know why so we can also
16 compare to our drug and see if our drug has the
17 same characteristics or potentially will have the
18 same characteristics.

19 Q. All things being equal, Abbott would
20 prefer to see a competitor MMPI demonstrate
21 efficacy with respect to certain kinds of cancers,
22 right?

23 A. No.

24 Q. Did Abbott view the failure of

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 prinomastat in certain Phase III trials as good or
2 bad?

3 MR. PHILLIPS: Objection to the form.

4 BY THE WITNESS:

5 A. Multiple things in your question. So,
6 rephrase, please.

7 BY MR. ZWICKER:

8 Q. Did Abbott view the failure of
9 prinomastat in certain Phase III trials for lung
10 cancer and for prostate cancer as causing concern
11 with respect to 518?

12 MR. PHILLIPS: Object to the form.

13 BY THE WITNESS:

14 A. Causing concern, yes. But what I mean
15 by concern is we have to look at the -- at the risk
16 and the opportunity that this can bring.

17 BY MR. ZWICKER:

18 Q. Okay. So, let me put the question to
19 you this way: Within Abbott, as of August 2000,
20 was Abbott -- did Abbott view the failure of
21 prinomastat at this point as presenting more risks
22 or more benefits?

23 MR. PHILLIPS: Object to the form.

24 BY THE WITNESS:

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1 A. I would say more benefits because we
2 proceeded with 518. We -- we got funds and we went
3 into clinical trials for 518. So, the overall
4 balance was to move forward with development of
5 518.

6 BY MR. ZWICKER:

7 Q. Okay. So, then in your own -- in your
8 mind, it's your testimony today that the failure of
9 prinomastat in certain Phase III clinical trials
10 was a good change?

11 MR. PHILLIPS: Object to the form;
12 mischaracterizes the testimony.

13 BY THE WITNESS:

14 A. In my opinion we had a very good reason
15 to proceed with 518 and that 518 was attractive
16 candidate to move into clinical trial.

17 BY MR. ZWICKER:

18 Q. Okay. I appreciate your answer that
19 you, notwithstanding these results, determined to
20 move forward at that time.

21 But within Abbott was the failure of
22 prinomastat in these clinical trials viewed as a
23 negative development for 518?

24 MR. PHILLIPS: Object to the form.

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1 brings some risk, right?

2 MR. PHILLIPS: Object to the form.

3 BY THE WITNESS:

4 A. Failure of a competitor can bring some
5 risk, yes.

6 BY MR. ZWICKER:

7 Q. In August of 2000 was Abbott concerned
8 that several of its competitors had demonstrated
9 joint toxicity during clinical trials?

10 MR. PHILLIPS: Objection to the form.

11 BY THE WITNESS:

12 A. We were watching joint toxicity very
13 carefully.

14 BY MR. ZWICKER:

15 Q. Why?

16 A. Because it was a concern or it was an
17 adverse event that showed with competitors.
18 However, we believed that our compound has -- has a
19 high likelihood of not showing joint toxicity.

20 Q. Why?

21 A. Because of the chemical entity and its
22 selectivity. And that's -- I believe it was on one
23 of the slides that you showed me earlier that was
24 presented by the research group. That was one of

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 our tested -- to-be-tested hypotheses.

2 Q. Okay. So, fair to say that Abbott is

3 concerned about joint toxicity but that it believes

4 it has a compound that can address the problem?

5 A. That's right.

6 Q. In August of 2000, Abbott was also

7 preparing for the first clinical trial for ABT-518.

8 True?

9 And if it refreshes your recollection,

10 you can look at pages -- you can look at any part

11 of the document you want, obviously, but you can

12 look at pages -- page 9.

13 A. Maybe I can answer it with the timeline

14 on page 11, see if that would refresh my memory.

15 Q. Okay.

16 A. According to the timeline that's on

17 page 11, Phase I trial was planned for November.

18 Q. What were -- sorry.

19 A. Or proposed for November.

20 Q. What were the objectives of that trial?

21 A. To look at the safety and

22 pharmacokinetics of the product.

23 Q. And to establish a maximum tolerated

24 dose. Is that so?

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1 A. That's right. That's part of the
2 safety.

3 Q. And a maximum tolerated dose is the most
4 amount of compound that could be introduced into
5 the human body without intolerable side effects.
6 Is that how you would define maximum tolerated
7 dose?

8 A. Generally speaking, yes.

9 Q. Are you also looking, at least
10 secondarily, at efficacy?

11 A. No. Phase I trial cannot answer
12 efficacy questions.

13 Q. Whether or not it can answer efficacy,
14 are you looking to see whether cancer patients'
15 tumors are stabilized in a Phase I trial?

16 A. It will give you hints, but never --
17 never -- never clear.

18 Q. Did you have responsibility for
19 determining or for organizing the Phase I clinical
20 trial?

21 A. Yes.

22 Q. What was your responsibility?

23 A. To plan the trials, design the trials,
24 select the sites, be sure it starts on time, be

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 sure it doses appropriately and so on, completion
2 of the trial, reviewing the results, interpreting
3 the results.

4 Q. You wrote the protocol?

5 A. I don't write it. One of my staff would
6 have written it.

7 Q. You reviewed it?

8 A. I would have, yes.

9 Q. How much did the Phase I clinical trial
10 cost?

11 A. I don't recall. I don't recall how much
12 that trial cost. There may be some cost estimates
13 here.

14 Q. Okay.

15 MR. PHILLIPS: I'm sorry, counsel. You're
16 asking in fact, what it actually cost as opposed to
17 what it was proposed?

18 MR. ZWICKER: That's a fair objection.

19 MR. PHILLIPS: I didn't mean -- it was
20 actually an inquiry.

21 BY THE WITNESS:

22 A. You want in general what a Phase I trial
23 costs?

24 BY MR. ZWICKER:

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1 Q. How much did -- what was the projected
2 cost for this clinical trial?

3 A. I don't recall this particular trial.

4 Q. Turn to page 8 of the document. There
5 is a discussion of toxicology.

6 MR. PHILLIPS: I'm sorry, counsel. What page?

7 MR. ZWICKER: Page 10. I'm sorry. Page 8.

8 MR. PHILLIPS: Thank you.

9 BY THE WITNESS:

10 A. Do you want me to read the toxicology
11 part?

12 BY MR. ZWICKER:

13 Q. Sure.

14 A. Okay.

15 Q. Okay. What was the role of toxicology
16 with respect to the development of ABT-518?

17 MR. PHILLIPS: Object to the form.

18 BY THE WITNESS:

19 A. Well, nothing specific -- you do
20 toxicology for any compound to ensure a safe -- a
21 safe starting dose in humans.

22 BY MR. ZWICKER:

23 Q. Toxicology is viewed as a preclinical
24 component of development?

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1 A. That's right.

2 Q. Animal testing?

3 A. Animal testing.

4 Q. In a sense it's the -- provides a
5 gate-keeping function regarding whether or not a
6 drug can be introduced to humans based on animal
7 testing?

8 MR. PHILLIPS: Objection.

9 BY MR. ZWICKER:

10 Q. Is that fair?

11 MR. PHILLIPS: I'm sorry. Objection to the
12 form.

13 BY THE WITNESS:

14 A. That's very broad. I cannot answer yes
15 or no.

16 BY MR. ZWICKER:

17 Q. How does -- the first sentence on page 8
18 under "Toxicology Program" says, "The toxicology
19 program has been designed to provide the data
20 required to support the Phase I clinical program."

21 Can you explain what that sentence
22 means?

23 A. The sentence would mean that we will do
24 toxicology work that will be appropriate for

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1 ensuring the initiation of Phase I, to give us the
2 appropriate starting dose, to give us the
3 appropriate dose range, in the clinic -- in the
4 first clinical study in humans.

5 We at that time have not put forward the
6 full toxicology program to support the full
7 development.

8 Q. You would agree with me that successful
9 completion of the toxicology program is important
10 to a successful Phase I clinical trial?

11 MR. PHILLIPS: Object to the form.

12 BY THE WITNESS:

13 A. No, I cannot say that. You -- we
14 need -- in any drug, we need to do appropriate
15 toxicology to ensure ourselves, to ensure the
16 regulators, to ensure the ethics committees and the
17 patients that the drug is appropriately
18 characterized from a safety perspective to be given
19 to the patients and to be dosed at appropriate
20 range in the patients population.

21 BY MR. ZWICKER:

22 Q. Do the toxicology and clinical 1 --
23 clinical Phase I trials proceed together sometimes?

24 A. You need toxicology before you start

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1 Phase I, but you could be doing additional studies

2 during Phase I to look for beyond Phase I.

3 Q. And that's what happened with 518,

4 wasn't it?

5 A. Probably. I don't recall how exactly

6 the program was designed for 518. It depends how

7 it was designed over time.

8 MR. ZWICKER: It's an old label.

9 MR. PHILLIPS: So we are remarking it?

10 MR. ZWICKER: Yes. In that instance anyway.

11 MR. PHILLIPS: Okay.

12 (WHEREUPON, a certain document was

13 marked Nabulsi Deposition Exhibit

14 No. 4, for identification, as of

15 01-24-2007.)

16 MR. ZWICKER: The record should reflect that

17 before the witness is Nabulsi Exhibit No. 4, which

18 is titled "MMPI Working Group Minutes, November 30,

19 2000."

20 BY MR. ZWICKER:

21 Q. Dr. Nabulsi, do you recognize this

22 document?

23 A. This type of document.

24 Q. What is it?

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 one.

2 (WHEREUPON, a certain document was

3 marked Nabulsi Deposition Exhibit

4 No. 6, for identification, as of

5 01-24-2007.)

6 MR. ZWICKER: The record should reflect that

7 before the witness is Nabulsi Exhibit No. 6, which

8 is the February 2001 report for ABT-518.

9 BY MR. ZWICKER:

10 Q. Do you have that, Dr. Nabulsi?

11 A. Yes.

12 Q. Do you recognize this document?

13 A. This type of document, yes.

14 Q. Forgive me, but did you say that it

15 would have been Diane D'Amico's responsibility to

16 compile monthly highlight reports?

17 A. She would have put the information --

18 this is a monthly highlight, right? There were a

19 lot of other documents like that. So, she would

20 have inputted into this document, but the final

21 compilation and preparation would have been the

22 operation manager. Don't recall who was the

23 operation manager. Maybe Bob Hansen was the

24 operation manager at the time.

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1 Q. Let me make sure I understand.

2 So, Ms. D'Amico's responsibility would
3 be to compile information from other places and put
4 them into the document?

5 A. That's right, as relevant to -- to what
6 she's doing. I mean, for instance, she did not
7 put -- she did not -- I'm just trying to refresh my
8 memory on some of the -- yeah, she would have --
9 she would have updated this document and then give
10 it to the operation manager to ensure accuracy and
11 then I would have reviewed it, yes.

12 Q. Okay. So, her job is to draw materials
13 from various sources, put the document together,
14 pass it on to Bob Hansen and then you would review
15 it, is that the process?

16 A. As I recall, yeah.

17 Q. Okay. This document is dated
18 February 2001. Do you see that?

19 A. Yes.

20 Q. Does the document purport to capture the
21 project status through the end of February 2001?

22 MR. PHILLIPS: Object to the form.

23 BY THE WITNESS:

24 A. I recall that the documents reported the

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 prior month.

2 BY MR. ZWICKER:

3 Q. So, this would be a report that had

4 status information for January?

5 A. It could be or it could be a report that

6 was issued March reporting February. I don't

7 recall.

8 Q. Okay. Turn to page 3 of 3, which is the

9 page entitled "Key Project Issues and Risks." Do

10 you see that?

11 A. Yes.

12 Q. Whose job would it have been to compile

13 the update with respect to competitor information?

14 A. Would have been gathered from -- by

15 Diane or Bob from research, from new project

16 planning and from the clinical team. So, from the

17 project team as a whole.

18 Q. Whose responsibility was it to obtain

19 the most up-to-date information regarding the

20 status of the MMPI competitors in February of 2001?

21 A. Again, would have been the job of the

22 senior project manager and the operation manager to

23 ensure gathering this information from the project

24 team members.

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 Q. Who was the senior project manager in
2 February of 2001?

3 A. I believe it was Diane at the time,
4 Diane D'Amico.

5 Q. And the operation manager was Hansen?

6 A. I believe was Hansen at the time.

7 Q. Now, Dr. Nabulsi, we've looked at
8 several documents that have summarized information
9 known to Abbott regarding the MMPI competitors.
10 Fair enough?

11 A. Yes.

12 Q. This morning.

13 A. Yes.

14 Q. This document summarizes information
15 known to Abbott as of February 2001 with respect to
16 only two of the competitors, prinomastat and
17 marimastat, is that right?

18 A. Let me look at that to be sure.

19 Q. Sure. Take your time.

20 MR. PHILLIPS: I'll object to the form.

21 BY THE WITNESS:

22 A. The question again.

23 BY MR. ZWICKER:

24 Q. The February 2001 monthly highlight

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 report summarizes information known to Abbott with
2 respect to only two compounds, prinomastat and
3 marimastat. Do you see that?

4 A. There are only two compounds listed
5 here, yes.

6 Q. And, sir, isn't it true that those two
7 compounds as of February 2001 were the most
8 important compounds to Abbott in assessing the
9 probability of success for 518?

10 MR. PHILLIPS: Objection to the form.

11 BY THE WITNESS:

12 A. I cannot say yes to that because that
13 could have been just the most recent -- the
14 compounds with the most recent events to the issue
15 of this report.

16 BY MR. ZWICKER:

17 Q. Sir, you would agree with me that you
18 and I today have not yet ever seen a document that
19 discusses in detail any more than four MMPI
20 competitor compounds, correct?

21 A. Today I have not seen any document.

22 Q. Now, this document contains some pretty
23 important news with respect to marimastat, isn't
24 that right?

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 MR. PHILLIPS: Objection to the form.

2 BY THE WITNESS:

3 A. Depend how you define "important." But

4 this is -- this is a development, a significant

5 development for marimastat.

6 BY MR. ZWICKER:

7 Q. Yeah. In fact, Abbott is reporting that

8 on February the 15th, 2001, marimastat development

9 was discontinued, right?

10 A. You said 2/15/01?

11 Q. Correct.

12 A. That's right.

13 Q. And that was an important development as

14 far as Abbott was concerned, wasn't it?

15 MR. PHILLIPS: Object to the form.

16 BY THE WITNESS:

17 A. This -- it's important.

18 BY MR. ZWICKER:

19 Q. Why was it important?

20 A. Again, because anything that happens to

21 the competition is important to know to do a better

22 job on 518.

23 Q. And, sir, did you view the termination

24 of development of marimastat as a negative factor

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1 for 518?

2 A. It was a concerning factor based on what
3 we discussed. So, to me this makes me more
4 watchful but at the same time, more optimistic. If
5 we are able to maneuver through the pitfalls of the
6 other compounds, we could have the best in class.

7 Q. This is your personal opinion at the
8 time, correct?

9 A. That's right. That's why I was always
10 moving forward and championing continuing the
11 development of 518.

12 Q. Sir, I appreciate your passion for the
13 compound. But did other persons in Abbott view the
14 discontinuance of the marimastat compound as a
15 negative factor for the development of 518?

16 MR. PHILLIPS: Objection to the preamble to
17 the question as argumentative. Object to the form.

18 MR. ZWICKER: Let me restate it.

19 BY MR. ZWICKER:

20 Q. Did other persons in Abbott as of
21 February 15, 2001, view the discontinuance of
22 marimastat as a negative factor for the development
23 of 518?

24 MR. PHILLIPS: Object to the form.

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1 BY THE WITNESS:

2 A. It's very broad. I don't know. The
3 people I was interacting with, my direct
4 management, we wanted to continue. That's why we
5 continued.

6 BY MR. ZWICKER:

7 Q. So, Dr. Nabulsi, as of 2/15/2001, with
8 respect to the four compounds that you've been
9 tracking in the documents we reviewed, the
10 following is true: First, development of
11 marimastat was discontinued on February 15, 2001,
12 correct?

13 A. It was discontinued according to this
14 document, yes.

15 Q. The Bayer drug known as tanomastat was
16 discontinued in approximately May of 2000, correct?

17 MR. PHILLIPS: Object to the form.

18 BY THE WITNESS:

19 A. I don't recall the date, but it was
20 discontinued prior to Pfizer.

21 BY MR. ZWICKER:

22 Q. And the prinomastat drug discontinued
23 certain Phase III trials with respect to pancreatic
24 cancer and non-small cell lung cancer. True?

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 MR. PHILLIPS: Object to the form.

2 BY MR. ZWICKER:

3 Q. Let me restate that question.

4 A. Um-hmm.

5 Q. With respect to prinomastat, the Pfizer
6 drug, Abbott knew as of August the 4th, 2000, that
7 Pfizer had discontinued Phase III trials with
8 respect to certain kinds of prostate cancer and
9 certain kinds of lung cancer. True?

10 A. According to one of these documents,
11 yes.

12 Q. And as of February 2001, Abbott does not
13 have efficacy data relating to the BMS MMPI drug,
14 does it?

15 MR. PHILLIPS: Object to the form.

16 BY THE WITNESS:

17 A. According to one of the documents I've
18 seen BMS did -- there were no efficacy data on BMS.

19 BY MR. ZWICKER:

20 Q. And all of the four MMPI compounds that
21 you've been tracking are demonstrating evidence of
22 joint toxicity, right?

23 MR. PHILLIPS: Object to the form.

24 BY THE WITNESS:

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1 A. No. Because we only see four here --

2 BY MR. ZWICKER:

3 Q. I just asked about those four.

4 A. These four? Bayer did not have joint

5 toxicity according to one of the tables.

6 Q. You're correct, sir. My apologies.

7 And the Bayer drug had been terminated,

8 right?

9 A. According to one of these documents,

10 yes.

11 Q. And, sir, your feeling in February 2001

12 that notwithstanding these results, you are feeling

13 optimistic about the prospects of success for 518?

14 A. Yes. Because we believed that we have a

15 better profile than the competition.

16 MR. ZWICKER: I'm going to mark two exhibits,

17 7 and 8.

18 (WHEREUPON, certain documents were

19 marked Nabulsi Deposition Exhibit

20 Nos. 7 and 8, for identification,

21 as of 01-24-2007.)

22 MR. ZWICKER: Okay. They are 7 and 8 in this

23 order.

24 The record should reflect that before

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 agenda?

2 MR. PHILLIPS: Object to the form.

3 BY THE WITNESS:

4 A. No. I have a question, though. I don't

5 know if it's a question. These are same dates,

6 different locations.

7 BY MR. ZWICKER:

8 Q. That's true. But my question to you is

9 do you know why 518 was added to the agenda?

10 A. No.

11 MR. ZWICKER: Nine.

12 (WHEREUPON, a certain document was

13 marked Nabulsi Deposition Exhibit

14 No. 9, for identification, as of

15 01-24-2007.)

16 MR. PHILLIPS: Is this -- is this my copy?

17 MR. ZWICKER: The record should reflect that

18 before the witness is Nabulsi Exhibit No. 9, which

19 is -- are certain slides from an Abbott portfolio

20 review dated March 7 through 9, 2001.

21 BY MR. ZWICKER:

22 Q. Dr. Nabulsi, do you recognize this

23 document?

24 A. Yes.

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 Q. What is it?

2 A. This is the portfolio review template

3 document that we used for the first -- I believe it
4 was the first year portfolio review.

5 Q. Who prepared these slides?

6 A. My team would have created the first
7 draft and then Bob Hansen and myself completed
8 the -- completed the presentation in its final
9 form.

10 Q. Were the -- was the presentation
11 distributed to senior management before the
12 portfolio review?

13 A. It was sent to -- we sent it to -- I
14 forgot the name, whoever organized the meeting.
15 I'm not sure how he distributed, what timing he
16 distributed. But it was sent to the -- was sent to
17 the organizer of the portfolio meeting.

18 Q. Who was the organizer of the portfolio
19 meeting?

20 A. I don't recall the name now.

21 Q. Do you know whether these slides were
22 presented to Dr. Leiden in advance of the meeting?

23 A. No.

24 Q. You attended this meeting, didn't you?

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 A. Yes.

2 Q. And some of the other attendees of the

3 meeting included Jeff Leiden, correct?

4 A. That's right.

5 Q. Bill Dempsey?

6 A. I don't recall if Bill was sitting in

7 that meeting or not.

8 Q. John Leonard?

9 A. Yes.

10 Q. Eugene Sun?

11 A. I don't recall if Eugene was in that

12 meeting or not.

13 Q. Marlene Verlinden?

14 A. I don't recall again.

15 Q. And Perry Nisen attended, correct?

16 A. Yes, yes.

17 Q. The first page of the project review has

18 a line known as "Presenter." Do you see that?

19 A. Yes.

20 Q. It says, "Perry Nisen"?

21 A. Correct.

22 Q. Did Perry Nisen make the presentation

23 regarding 518 --

24 A. Yes.

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 Q. -- at the portfolio review?

2 A. Yes.

3 Q. Did you speak at all?

4 A. Yes.

5 Q. Did anybody besides you and Perry Nisen
6 speak on 518?

7 A. I don't -- I don't recall.

8 Q. If you look at the last line of the
9 first slide where it says "Project Team Members,"
10 it says, "T. Janus."

11 Do you see that?

12 A. Yes.

13 Q. That's Todd Janus, right?

14 A. Correct.

15 Q. Did he attend?

16 A. I don't recall now.

17 Q. Next is D. D'Amico. That's Diane
18 D'Amico?

19 A. Yes.

20 Q. Did she attend?

21 A. Probably not.

22 Q. Turn to page 2 of the document. It's
23 entitled "Key" -- pre- -- "Key Preclinical
24 Findings."

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 Do you see that?

2 A. Yes.

3 Q. There's a line for "Toxicology." Could

4 you look at that?

5 A. Yes.

6 Q. Who presented the portion of the

7 presentation relating to toxicology?

8 A. Would have been Perry that presented the

9 whole content, if I recall.

10 Q. For the preclinical findings?

11 A. Yeah, I believe in that meeting we did

12 not cut the pieces between different members. I

13 believe he presented the whole thing.

14 Q. For preclinical?

15 A. That's right.

16 Q. And you would agree with me that as of

17 March 7, 2001, that ABT-518 did not present any

18 concerns regarding toxicology?

19 A. That's right.

20 Q. Turn -- this is unfortunate -- to the

21 document titled ABBT 13228, which unfortunately is

22 also titled page 1. But it's several pages on and

23 it's called "Phase I Study."

24 A. Okay.

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 Q. Okay. Do you know Perry Nisen well?

2 A. Yeah, I know him well.

3 Q. Do you think of him as a thorough and
4 complete reporter of events that are within his
5 purview of responsibility?

6 MR. PHILLIPS: Object to the form.

7 BY THE WITNESS:

8 A. That's very broad.

9 BY MR. ZWICKER:

10 Q. Let me ask you a different question.

11 Did you -- you sat through Perry Nisen's
12 presentation --

13 A. That's right.

14 Q. -- on competitive data, right?

15 A. That's right.

16 Q. Sitting here today do you recall that he
17 gave a full and complete rendition of the status of
18 the MMPI competitors?

19 A. I believe --

20 MR. PHILLIPS: Object to the form.

21 BY THE WITNESS:

22 A. I believe Perry was fair and -- and
23 accurate at the time, yes.

24 BY MR. ZWICKER:

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1 Q. Okay. Do you have any doubt in your
2 mind that Perry Nisen told Jeff Leiden and others
3 that the marimastat drug had been discontinued in
4 February of '01?

5 A. I don't remember the exact specifics,
6 but Perry would have been thorough and fair in his
7 assessment.

8 Q. And that would have included giving him
9 an update on the marimastat drug, correct?

10 A. You ask me to guess.

11 Q. I don't want you to guess.

12 A. Yeah. He would have included what he
13 knew about all the competitive compounds.

14 Q. And you agree with me that one of the
15 things that Abbott knew about marimastat was that
16 it had been discontinued in February. True?

17 MR. PHILLIPS: Object to the form.

18 BY THE WITNESS:

19 A. Anything that he knew by that time of
20 this presentation he would have disclosed.

21 BY MR. ZWICKER:

22 Q. So, you would also agree with me that
23 Perry Nisen would have disclosed to Jeff Leiden
24 that the Bayer drug, tanomastat, had been

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1 discontinued as well?

2 MR. PHILLIPS: Object to the form.

3 BY THE WITNESS:

4 A. That compound discontinued in February.

5 So, by the time of that presentation, Perry would

6 have known that and he would have shared that.

7 BY MR. ZWICKER:

8 Q. And you agree with me that Perry would
9 have shared the bad data relating to prinomastat's
10 efficacy with respect to certain kinds of cancers
11 as well. True?

12 MR. PHILLIPS: Object to the form.

13 BY THE WITNESS:

14 A. You know, everything we have seen on the
15 slide before in relation to these four compounds
16 was -- was presented in the company. So it would
17 not have been -- the portfolio review would not
18 have been the first chance.

19 I mean, multiple slides you have seen
20 that were shared in the company about the
21 competition.

22 BY MR. ZWICKER:

23 Q. I appreciate that. I'm just asking you
24 whether you have any doubt that Perry Nisen relayed

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1 that data to Jeff Leiden.

2 A. I have no doubt, no.

3 One thing I'd like to mention, based on
4 the nature of this presentation, you have the
5 potential issues, threats and risks, but above that
6 you have the strengths and positives.

7 Q. I see that.

8 A. So, that's the equation I mentioned
9 earlier.

10 Q. I see that.

11 I take it you also have no doubt that
12 Perry Nisen informed Dr. Leiden about joint
13 toxicity issues in many of the competitive
14 compounds as well. True?

15 MR. PHILLIPS: At this meeting?

16 MR. ZWICKER: At this meeting.

17 BY THE WITNESS:

18 A. Perry would have shared the joint
19 toxicity at this meeting, toxicity issues with the
20 competitors at this meeting.

21 BY MR. ZWICKER:

22 Q. Did you participate at all in the
23 summary of competitor data on March 7, 2001?

24 MR. PHILLIPS: Objection to the form.

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1 MR. ZWICKER: Let me rephrase it. It's a fair
2 objection.

3 BY MR. ZWICKER:

4 Q. Did you add to or detract from Perry
5 Nisen's presentation regarding competitor data on
6 March 7?

7 A. I did not speak as to the competitor
8 data on March 7.

9 Q. Dr. Nabulsi, isn't it a fact that after
10 Jeff Leiden heard that summary, he posed the
11 question to you and to Dr. Nisen: "How can we
12 continue if our competition is dropping out"?

13 A. I don't remember the exact words, but he
14 did ask about our logic for continuation.

15 Q. You said you don't remember his exact
16 words. What do you remember about what he said?

17 A. That he asked for our reasoning for
18 continuing and why he should support continuing in
19 relation to the competition situation.

20 Q. So, is it fair to say that having heard
21 the competitor data, Dr. Leiden expressed some
22 skepticism regarding whether or not the 518 program
23 should continue. Is that fair?

24 A. He expressed concern about continuing

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 518.

2 Q. Would you say he expressed doubt about

3 whether to continue developing 518?

4 MR. PHILLIPS: Object to the form.

5 BY THE WITNESS:

6 A. I don't know if I can say doubt. He

7 expressed concern, concern about continuing. He

8 challenged us to tell him why we should continue.

9 BY MR. ZWICKER:

10 Q. Did he express to you and Dr. Nisen any

11 pessimism regarding the prospects for 518 at the

12 meeting on March the 7th?

13 A. Did he -- can you repeat that? I want

14 to be sure I answer it correctly.

15 Q. In your view, sir, was Dr. Leiden

16 pessimistic on March 7, 2001 regarding the

17 prospects for 518, having heard the presentation on

18 competitor data?

19 MR. PHILLIPS: Object to the form.

20 BY THE WITNESS:

21 A. He was pessimistic.

22 BY MR. ZWICKER:

23 Q. On March the 7th, 2001, did Dr. Leiden

24 direct you and Dr. Nisen to discontinue and

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1 terminate all development activities relating to
2 518?

3 A. No.

4 Q. On March 7, 2001, did Dr. Leiden invite
5 you and Dr. Nisen to make a presentation to him
6 regarding why development of 518 should continue?

7 MR. PHILLIPS: Object to the form.

8 BY THE WITNESS:

9 A. On March 7, during that meeting, no.

10 BY MR. ZWICKER:

11 Q. When Dr. Leiden expressed pessimism
12 regarding the development of 518, what did you say?

13 A. We reiterated the positive view that
14 this still has a good likelihood of being
15 successful candidate because it does not have -- we
16 don't believe it has the characteristics that the
17 other compounds have which may have caused them to
18 discontinue, characteristics that were preclinical,
19 and also we explained that their development
20 programs were too aggressive and may be ill planned
21 and, hence, resulted in their failure.

22 Because of those reasons, we said we
23 can, you know -- we probably have a better
24 candidate, we can do better development plan and we

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1 have chances of success. And we asked to continue
2 knowing that the Phase I study could be a very good
3 study and give us an indication if this drug is
4 safe or not.

5 Q. Did you --

6 A. And that was one key milestone.

7 Q. I'm sorry. What was the last thing you
8 said?

9 A. That it is a key milestone in making an
10 informed decision.

11 Q. Was that a presentation that you made as
12 well on March the 7th?

13 A. That was discussion.

14 Q. That you participated in?

15 A. That I participated in.

16 Q. Along with Perry Nisen?

17 A. Along with Perry Nisen.

18 Q. What was Dr. Leiden's response to the
19 presentation you made to continue development of
20 518, notwithstanding the adverse competitor data?

21 A. He asked about the cost for Phase I
22 study.

23 Q. What did you say?

24 A. I replied with the cost for the Phase I

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1 study.

2 Q. Which you knew at the time?

3 A. Which I knew at the time.

4 Q. But can't remember today?

5 A. I can't remember today.

6 Q. What else did he say?

7 A. I believe that concluded the discussion.

8 Q. So, as of March 7, 2001, Dr. Leiden had

9 not indicated to you one way or another whether he

10 had decided to continue development of 518?

11 A. When I left the meeting, I don't recall

12 that there was a decision to discontinue 518.

13 Q. Did you discuss -- immediately after the
14 meeting, did you discuss Dr. Leiden's pessimism
15 with Perry Nisen?

16 A. I don't recall vividly, but we must have
17 talked about it.

18 Q. Do you remember the gist of what you
19 talked about?

20 A. No. I mean probably reiterated our
21 commitment to continue.

22 Q. Were you pessimistic of -- were you
23 pessimistic about how Dr. Leiden would decide
24 whether to continue the development or not?

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1 portfolio review on March 7?

2 A. I don't recall sitting in a meeting, but
3 we probably had an update meeting to report on the
4 portfolio review.

5 MR. ZWICKER: Let's mark these as the next
6 two.

7 (WHEREUPON, certain documents were
8 marked Nabulsi Deposition Exhibit
9 Nos. 10 and 11, for identification,
10 as of 01-24-2007.)

11 BY MR. ZWICKER:

12 Q. Dr. Nabulsi, let's begin with Nabulsi
13 Exhibit No. 10, which is a meeting agenda for the
14 MMPI monthly meeting, March 8, 2001, and it bears
15 Bates stamp No. ABBT 45253.

16 Do you have that in front of you?

17 A. Yes.

18 Q. Do you recognize the handwriting on that
19 document?

20 A. Yes.

21 Q. Whose?

22 A. I believe this is Diane D'Amico's.

23 Q. Can you review this document and let me
24 know whether it refreshes your recollection of the

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1 March 8, 2001 MMPI monthly meeting.

2 A. Yeah, I recall the meeting.

3 Q. You recall the meeting.

4 MR. PHILLIPS: You have to respond orally.

5 BY THE WITNESS:

6 A. I'm sorry. I was still looking.

7 Yes, I recall such meeting.

8 BY MR. ZWICKER:

9 Q. And if you look at I, it says

10 "Clinical," it has your name.

11 A. Um-hmm.

12 Q. Is it -- am I pronouncing this right?

13 Is it Azmi?

14 A. Azmi, yeah.

15 Q. Azmi Nabulsi and Diane D'Amico.

16 A. D'Amico.

17 Q. D'Amico. Were you the person that --

18 and the line below it is, "Leiden portfolio review

19 3/7"?

20 A. Yes.

21 Q. Do you see that?

22 A. Yes.

23 Q. Were you the person that made the

24 presentation to the group regarding the Leiden

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1 portfolio review on March 7?

2 A. Most likely.

3 Q. What do you remember telling the group

4 regarding the Leiden portfolio review on March 7?

5 A. The key things were that we are to

6 continue the development and -- this refreshing my

7 memory here.

8 Basically I described to them the

9 question that Jeff brought up, and I'm describing

10 to them the answer to that question that Perry and

11 I gave during the meeting.

12 And this is what I recall now that we

13 were asked to watch further for the competition

14 especially as relates to the upcoming meeting at

15 ASCO -- meetings at ASCO and AACR to see if there

16 are additional new data that will come up from

17 other or the current MMPIs that will shed more

18 light on the class.

19 Q. The first line in handwriting says, "How

20 can we continue if competition is dropping out?"

21 Do you see that?

22 A. Yes.

23 Q. Is that your summary of what Dr. Leiden

24 said?

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1 A. I believe so.

2 Q. And then the next portion you say

3 relates to your presentation to Dr. Leiden on

4 March 7 regarding why you and Dr. Nisen believed

5 that you ought to continue, is that right?

6 A. This -- this was at the time our

7 reasoning, yes. Whether I gave it, all of it or

8 Perry and I, I mean I don't recall who spoke the

9 words. But this was our reasoning at the time,

10 yes, during that meeting.

11 Q. The handwriting says, and I appreciate

12 it's not yours, "Comp too low doses." Do you see

13 that?

14 A. Yes.

15 Q. Do you know what that means?

16 A. Yeah.

17 Q. What?

18 A. That the competition may have dosed at

19 lower doses than needed to be efficacious.

20 Q. The next line says, "Mono versus combo"?

21 A. That's right.

22 Q. Do you know what that relates to?

23 A. That again the competition --

24 competitors' studies were using their MMPIs as mono

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1 therapy, which is the one drug, as opposed to
2 combination with other cancer drugs.

3 Q. Did you say to Dr. Leiden on March the
4 7th that one use of 518 could be in combination
5 with other drugs?

6 A. We must have, yeah.

7 Q. The next line is "Skipped Phase II"?

8 A. That's right.

9 Q. What drug are you -- what compound are
10 you talking about?

11 A. I believe that was the Bayer compound,
12 that they did not do Phase II. Most of these
13 compounds did not. But I believe that may have
14 been to the -- related to the Bayer compound. I
15 don't recall the specifics but...

16 Q. Okay. And then you say, "Not right
17 stage tumors." What does that mean?

18 A. That the competitors may not have been
19 studying their compounds in the appropriate tumor
20 stage, that they were looking at much later stage
21 disease that will -- that created a much more
22 difficult test for their -- for the MMPIs and that
23 the MMPIs may be needed to be studied in earlier
24 stage disease to give them higher chance of

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1 demonstrating efficacy.

2 Q. And then the next line is, "We'll look

3 at ASCO and AACR for comp info."

4 Do you see that?

5 A. Yes.

6 Q. What are you saying here?

7 A. So, I'm saying that we -- we are to

8 watch carefully for additional data in future

9 upcoming scientific meetings.

10 I believe one of the things that Jeff

11 Leiden want us to be very careful and watchful of

12 what comes out because any additional new negative

13 data would increase his pessimism.

14 I can't pronounce it.

15 Q. This is Jeff Leiden's view that new bad

16 data increases pessimism?

17 MR. PHILLIPS: Object to the form.

18 BY THE WITNESS:

19 A. That was the challenge to us, that as an

20 outcome of the meeting we continue but we have to

21 be watchful of what other data comes -- comes out.

22 BY MR. ZWICKER:

23 Q. When you say the outcome of the meeting,

24 you mean this was the presentation you gave to

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1 Dr. Leiden to continue development on March 7?

2 A. That's right. I believe that was the

3 conclusion of that meeting with Jeff Leiden that I

4 was reporting on here.

5 Q. With respect to competitor data, you

6 knew on March 7 that the Bayer compound had been

7 terminated, right?

8 MR. PHILLIPS: Objection; asked and answered.

9 BY THE WITNESS:

10 A. If I recall, Bayer was the one

11 terminated in February or so?

12 BY MR. ZWICKER:

13 Q. May of 2000, thereabouts.

14 A. May. Yeah.

15 Q. And you knew that the marimastat

16 compound had been terminated, correct?

17 MR. PHILLIPS: Object to the form.

18 BY THE WITNESS:

19 A. I knew that marimastat was terminated.

20 BY MR. ZWICKER:

21 Q. And you had no data with respect to the

22 BMS compound, right?

23 MR. PHILLIPS: Object to the form.

24 BY THE WITNESS:

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1 at the document. If that's what the document is
2 saying and we reported it, then we must have known
3 it.

4 BY MR. ZWICKER:

5 Q. So, tell me, sir, exactly on March 7
6 what it is you were waiting for from the
7 competitors.

8 A. There were additional studies that were
9 still ongoing for the competitors and studies that
10 were completed by the competitors but have not been
11 reported. I don't remember the specifics. But
12 there were still MMPIs in development.

13 Q. Okay. But of the four that you were
14 tracking in the documents we have seen, two had
15 been terminated, right?

16 A. That's right. But sometimes, you know,
17 something is terminated from a press release but
18 you don't know what the nature of the data. So,
19 you cannot really make any assessment other than
20 knowing a press release information.

21 So, you wait for -- for a publication, a
22 presentation, some scientific public information so
23 you can make a judgment.

24 Q. Okay. So, it was your view and

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1 Dr. Nisen's view to await the results of the
2 competitor data for the four competitors you were
3 tracking?

4 MR. PHILLIPS: Object to the form.

5 BY THE WITNESS:

6 A. I cannot answer that. I don't recall
7 exactly. We knew -- what I recall, that we knew
8 there were additional data that we need from the
9 competitor to increase our ability to make
10 decisions. And we needed data. So, we cannot make
11 reactions and decision based on a press release if
12 it was the data not complete.

13 So we knew there -- ASCO is like the big
14 trade show. That is where new stuff comes out in
15 more details and -- and when it's presented, you
16 have a chance to talk to scientists about it. You
17 have a chance to talk to opinion leaders about it
18 so you learn a lot. And you get out of those
19 meetings, you be able to make decisions if what you
20 learn dictates that.

21 Q. Okay. Turn to Exhibit No. 8, which are
22 the minutes from the --

23 MR. PHILLIPS: I'm sorry, counsel. I think
24 you are reading the wrong --

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1 BY MR. ZWICKER:

2 Q. You made a pitch to Dr. Leiden on

3 March the 7th that notwithstanding the adverse data

4 from the competitors that development of 518 should

5 continue, correct?

6 MR. PHILLIPS: Object to the form.

7 BY THE WITNESS:

8 A. We -- we argued to continue 518.

9 BY MR. ZWICKER:

10 Q. Okay. And, sir, isn't it a fact that on

11 or about March 9th Dr. Leiden rejected your

12 recommendation and immediately directed a halt to

13 all development activities relating to ABT-518?

14 MR. PHILLIPS: Object to the form, compound.

15 BY THE WITNESS:

16 A. I don't recall the exact date, but in

17 the -- after that meeting, I don't know if it's a

18 day or a week or two weeks, after that meeting, the

19 March 7th meeting, we were asked to stop -- to stop

20 the Phase I. I don't recall if it was to stop all

21 development or stop the Phase I or so on. But we

22 were asked to stop the Phase I.

23 BY MR. ZWICKER:

24 Q. Okay. But, sir, isn't it true that you

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1 were directed to cease all development activities
2 for 518 by Dr. Leiden?

3 A. We were asked --

4 MR. PHILLIPS: Objection; asked and answered.

5 BY THE WITNESS:

6 A. We were asked to stop 518. I don't -- I
7 don't recall the exact nature and the language of
8 the order. It came to me through from Perry. I
9 never -- did not talk to Jeff Leiden directly.

10 MR. ZWICKER: Let's mark as the next exhibit
11 these two, and we're going to mark them in this
12 order.

13 (WHEREUPON, certain documents were
14 marked Nabulsi Deposition Exhibit
15 Nos. 12 and 13, for identification,
16 as of 01-24-2007.)

17 BY MR. ZWICKER:

18 Q. I'd like you, Dr. Nabulsi, to review
19 Nabulsi Exhibit No. 12, which is a typewritten
20 document to Jim from Azmi bearing Bates
21 No. ABBT0507886 and take a look at it.

22 MR. ZWICKER: Let's go off the record for one
23 minute.

24 THE VIDEOGRAPHER: Going off the record. The

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1 time now is 12:19.

2 (WHEREUPON, discussion was had off

3 the record.)

4 THE VIDEOGRAPHER: We're back on the record.

5 The time now is 12:19 p.m.

6 BY MR. ZWICKER:

7 Q. Review the document and let me know when

8 you're done.

9 THE VIDEOGRAPHER: Off the record at 12:20

10 p.m.

11 (WHEREUPON, discussion was had off

12 the record.)

13 THE VIDEOGRAPHER: We're back on the record at

14 12:21 p.m.

15 BY THE WITNESS:

16 A. Okay.

17 BY MR. ZWICKER:

18 Q. Dr. Nabulsi, is this a document that you

19 authored, Exhibit No. 12?

20 A. Yeah, I believe so. What date -- what's

21 the date on this?

22 Q. Well, it is undated.

23 A. Undated.

24 Q. But is it a document you authored?

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1 A. Yes.

2 Q. Was it authored in the form of an

3 e-mail?

4 A. I believe so.

5 Q. And it was a document that you authored

6 in connection with your duties and responsibilities

7 at Abbott, correct?

8 A. That's right.

9 Q. And, sir, to your knowledge, was it the

10 regular practice of Abbott to maintain records

11 relating to the development of compounds?

12 MR. PHILLIPS: Objection to the form.

13 BY THE WITNESS:

14 A. What do you mean? Not clear to me, your

15 question.

16 BY MR. ZWICKER:

17 Q. Was it Abbott's practice to keep and

18 maintain documents that related to compounds under

19 development?

20 MR. PHILLIPS: Object to the form.

21 BY THE WITNESS:

22 A. Very broad question. I mean, it's -- we

23 keep -- Abbott and the industry keep records as

24 regulated by -- by law and by agencies and so on.

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1 BY MR. ZWICKER:

2 Q. And it would have been Abbott's practice
3 to keep and maintain a document that you authored
4 relating to the development of 518, correct?

5 MR. PHILLIPS: Object to the form.

6 BY THE WITNESS:

7 A. This, again, is a very broad question
8 because you have documents, trial results, trial
9 information, regulatory documents. These are kept.
10 But mine are notes and so on.

11 BY MR. ZWICKER:

12 Q. To your knowledge, were your e-mails and
13 correspondence relating to 518 maintained by
14 Abbott?

15 MR. PHILLIPS: Object to the form.

16 BY THE WITNESS:

17 A. E-mails, whatever at the time e-mail
18 policy of Abbott would have been applied to my
19 e-mails as anyone's e-mails.

20 BY MR. ZWICKER:

21 Q. And, to your knowledge, they were
22 maintained?

23 A. There was a policy --

24 MR. PHILLIPS: Object to the form.

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1 BY THE WITNESS:

2 A. -- by Abbott to back up e-mails.

3 BY MR. ZWICKER:

4 Q. And Exhibit No. 12 is a document that

5 you authored in March of 2001 to the best of your

6 knowledge?

7 A. I don't recall the date. I recall

8 typing a document as such.

9 Q. Do you recall --

10 A. But I don't recall the date.

11 Q. Do you recall that this document was

12 typed at or near the March 7, 2001 portfolio

13 meeting?

14 MR. PHILLIPS: Object to the form.

15 BY THE WITNESS:

16 A. This -- this must have been -- this must

17 have been after we dosed the patients, because in

18 it I say that AZU is expecting a patient Monday

19 morning. So, we already dose patients.

20 So, if I track information from here, we

21 were dosing patients on or about March 12 I

22 believe.

23 BY MR. ZWICKER:

24 Q. Well, it says -- and I'm just asking you

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1 Q. Okay. So, the answer to my question is
2 that this document does refresh your recollection?

3 A. Yes, I recall that we asked to stop.

4 Q. Okay. So, is it fair, then, that within
5 a day or so of the March 7th meeting, you learned
6 that Dr. Leiden had directed that all development
7 activities for ABT-518 were to cease immediately.
8 True?

9 MR. PHILLIPS: Objection to the form.

10 BY THE WITNESS:

11 A. It's a -- too many things there.

12 BY MR. ZWICKER:

13 Q. Let me ask you a different question.

14 A. Uh-huh.

15 Q. Within a few days of the March 7th, 2001
16 portfolio meeting, you learned that Dr. Leiden
17 directed that all development activities for
18 ABT-518 were to be terminated immediately. True?

19 A. Within a few days and after dosing
20 patients, we learned to stop, yes.

21 Q. Who told you to cease all development
22 activities for ABT-518?

23 A. Perry reported to me.

24 Q. What did he tell you?

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- 1 A. That we were asked to stop immediately.
- 2 Q. Did he tell you that that was at
- 3 Dr. Leiden's instruction?
- 4 A. That's right.
- 5 Q. Did he tell you why Dr. Leiden gave that
- 6 instruction?
- 7 A. It was an outcome of his -- his concern
- 8 about the competition and that this compound,
- 9 chances of being successful are low.
- 10 Q. So, to your understanding, Dr. Leiden
- 11 rejected the presentation by you and Dr. Nisen to
- 12 distinguish 518 from the competitors. True?
- 13 A. That's right.
- 14 Q. This note is addressed to Jim. Is that
- 15 Jim Looman?
- 16 A. Yes.
- 17 Q. Who was he?
- 18 A. He was a medical director or at the time
- 19 maybe associate medical director working for me in
- 20 Netherlands, managing clinical trials in Europe.
- 21 Q. Now, when you say "We should stop all
- 22 development activities immediately," what
- 23 development activities did you intend to stop?
- 24 A. Well, the key thing for us here, what I

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1 was instructing him to stop the clinical trial, the
2 ongoing clinical trial, not to enroll new patients
3 in the clinical trial. And any other -- though
4 outside Jim, stopping development activity with me
5 and stop all efforts on the product.

6 Q. That would include toxicology?

7 A. Would include toxicology, CMC as well.

8 Q. What is CMC?

9 A. Chemical manufacturing, making drug.

10 Q. What about the -- were you aware that
11 there was an IND study underway in March of 2000?

12 MR. PHILLIPS: Object to the form.

13 BY THE WITNESS:

14 A. We were planning a U.S. study.

15 BY MR. ZWICKER:

16 Q. That's what I meant.

17 A. Yeah, yes.

18 Q. Would activities relating to that study
19 have been terminated as well?

20 MR. PHILLIPS: Object to the form.

21 BY THE WITNESS:

22 A. The -- that will be included in
23 development activity statement, yes.

24 BY MR. ZWICKER:

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1 Q. Were there any PK development activities
2 underway in or around March 7, 2001?

3 A. I don't recall. They would be part of
4 toxicology or any clinical work we do.

5 Q. But sitting here today, your testimony
6 is that on or about March 7, your instructions from
7 Dr. Leiden were to terminate all development
8 activities relating to 518. True?

9 MR. PHILLIPS: Object to the form.

10 BY THE WITNESS:

11 A. On or about March 8 or after March 8.

12 Because 8th I reported that we are to continue.

13 BY MR. ZWICKER:

14 Q. So, it would have been after March 8 but
15 before March 11. True?

16 A. Could have been after March 11 because I
17 don't -- I cannot tell from my e-mail here if that
18 was the first patient to be dosed or maybe we have
19 dosed some patients that were on the trial at the
20 time and that was a new patient.

21 Q. Dr. Nabulsi, take a look at
22 Exhibit No. 13, which is a chronology.

23 A. Um-hmm.

24 Q. Did you prepare this chronology?

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1 A. No. No. This is something

2 Abbott document?

3 Q. It is.

4 A. It's most likely Diane D'Amico prepared

5 this.

6 Q. Look at the entry for March 11, 2001.

7 It says, "Nabulsi (Oncology head, Abbott US) calls

8 Looman (assistant medical director oncology, Abbott

9 NL)," which I think is Netherlands, "to inform

10 about immediate stop of ABT-518 project (and thus

11 study M00-235) Janus (medical director oncology,

12 Abbott US) and D'Amico (PM, oncology, Abbott US)."

13 Do you see that?

14 A. Um-hmm.

15 Q. Sir, based on the chronology, do you

16 believe that you were instructed to cease all

17 development activities relating to ABT-518 at some

18 point prior to March 11?

19 MR. PHILLIPS: Object to the form.

20 BY THE WITNESS:

21 A. I was asked to stop on or -- I would

22 conclude from this between 8th and 11th.

23 BY MR. ZWICKER:

24 Q. Now, in your own mind, when you received

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1 the instruction from Perry Nisen to stop all
2 development activities, did you believe that
3 instruction was permanent?

4 MR. PHILLIPS: Object to the form.

5 MR. ZWICKER: Let me ask it again.

6 BY MR. ZWICKER:

7 Q. Did you believe that the termination of
8 development activities for ABT-518 was temporary or
9 permanent?

10 MR. PHILLIPS: Objection to the form.

11 BY THE WITNESS:

12 A. My discussion with Perry at the time
13 that we need to rechallenge the decision or the
14 instructions. So, whether it was permanent or not.
15 Obviously -- I don't know if it's the same between
16 permanent and terminate, but our decision was to
17 rechallenge.

18 BY MR. ZWICKER:

19 Q. Okay. But in your mind the instruction
20 from Dr. Leiden was not a temporary decision? It
21 was a permanent decision?

22 A. That's right.

23 MR. PHILLIPS: Objection. I'm sorry.

24 THE WITNESS: I'm sorry.

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1 MR. PHILLIPS: Dr. Nabulsi, please give me
2 just a moment.

3 THE WITNESS: Okay. Go ahead.

4 MR. PHILLIPS: Object to the form.

5 BY MR. ZWICKER:

6 Q. Go ahead and answer.

7 A. You don't stop a study and start again.

8 It's an -- it's an important event. We did not
9 know if Jeff understands that and what his clear
10 instructions. So we need to challenge. Our -- our
11 intention was to rechallenge his decision.

12 Q. But you took his directive as a final
13 decision to terminate the 518 program?

14 MR. PHILLIPS: Object to the form;
15 mischaracterizes the testimony.

16 BY THE WITNESS:

17 A. I don't recall how I took the decision.
18 I wasn't happy with the decision and we decide to
19 rechallenge it.

20 BY MR. ZWICKER:

21 Q. But in your own mind when you received
22 his instruction, you viewed his instruction as a
23 final decision. True?

24 MR. PHILLIPS: Object to the form; asked and

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1 Q. What else did they do?

2 A. They stayed on hold till further

3 instructions.

4 Q. To your knowledge, what did the sites do

5 with the patients that had already been enrolled?

6 A. I don't recall how many patients, but

7 that to continue dosing of the patients enrolled.

8 Q. They continued being dosed?

9 A. That's right.

10 Q. Did you instruct Jim Looman to provide

11 the sites with the reasons why the clinical trial

12 had been halted?

13 A. Yes.

14 Q. What did you tell Looman to say?

15 A. Prioritization and the competition

16 status.

17 Q. Did there come a time on or around the

18 12th of March when you personally had a

19 conversation with Professor Schellens?

20 A. What date? I'm sorry. Can you repeat

21 the date?

22 Q. On or around the 12th.

23 Let me strike that and go back one.

24 MR. ZWICKER: Let me mark as the next exhibit.

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1 (WHEREUPON, a certain document was
2 marked Nabulsi Deposition Exhibit
3 No. 14, for identification, as of
4 01-24-2007.)

5 MR. ZWICKER: The record should reflect that
6 marked as Nabulsi Exhibit No. 14 is an e-mail from
7 Diane D'Amico to various persons dated March the
8 12th, 2001.

9 BY MR. ZWICKER:

10 Q. Dr. Nabulsi, this is an e-mail from
11 Diane D'Amico to Professor Schellens that begins,
12 "As you know, we have been instructed to halt the
13 M00-235 study. I assume that you know that the AZU
14 enrolled a patient into the study today."

15 Do you recognize this document?

16 A. I don't recall the exact e-mail, but the
17 content makes sense to me.

18 Q. Did you instruct Diane D'Amico to
19 contact the sites and instruct them not to enroll
20 any additional patients?

21 A. That's right. That's my role and that's
22 her job, yes.

23 Q. Did you tell her to instruct the sites
24 that the halt on the study was permanent?

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1 A. No, no, probably not, because -- I don't

2 recall exactly what I told her.

3 Q. What's the best recollection of what you

4 told her?

5 A. My best recollection that I instructed

6 her to stop enrolling any new patients immediately.

7 Q. To instruct the sites to do that?

8 A. That's right.

9 Q. Did you explain to Diane D'Amico why it

10 was that she should instruct the sites not to

11 enroll any more patients?

12 A. You mean the reason of not enrolling or

13 why she --

14 Q. I will ask the it again.

15 A. Yeah.

16 Q. Did you -- did you tell Diane D'Amico

17 why it was that the study had been halted?

18 MR. PHILLIPS: Object to the form.

19 BY THE WITNESS:

20 A. I did tell Diane of the reasons similar

21 to what I have instructed Jim Looman or what I

22 communicated with Jim Looman on the reasons.

23 BY MR. ZWICKER:

24 Q. Namely, that Dr. Leiden had terminated

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1 of today, and Ms. D'Amico provides your name and
2 says that you will call in the morning. Is that
3 about a proper summary?

4 A. Dr. Schellens. You said Dr. Nabulsi.

5 Q. Ah, Schellens. Correct.

6 A. That's right.

7 Q. Do you recall having a conversation with
8 Professor Schellens, the first conversation you had
9 with him after the clinical trial had been halted?

10 A. I don't recall, you know, the actual
11 conversation. But I'm certain that I did talk to
12 him because that's my job, to communicate with him.

13 Q. What did you tell him about the reasons
14 for the shutdown of the clinical trial?

15 A. Would have been the same reasons, the
16 priority of the portfolio and the competition.

17 Q. What was his response?

18 A. He was very displeased.

19 Q. What did he say?

20 A. That this is not the appropriate thing
21 to do.

22 Q. What did he suggest doing instead?

23 A. That he still wanted to communicate with
24 Abbott highest ranking officer or highest ranking

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1 decision maker to inform them that this is not the
2 appropriate decision.

3 Q. Did you direct him to Dr. Leiden?

4 A. He knows of Dr. Leiden. I did not
5 direct him to Dr. Leiden. I said I'll handle it.

6 We are working on it to restart the study, and I
7 will get back to him to see what we are doing. I
8 just told him about our efforts internally to get
9 the study going.

10 Q. What did you tell him about your efforts
11 to get the study going?

12 A. That Perry and I believe the study
13 should continue, we believe in the compound, and
14 that Perry is -- is taking the necessary steps to
15 convince upper management to continue.

16 Q. And by "necessary steps," did you
17 understand that Perry Nisen would lobby Dr. Leiden
18 to continue development?

19 MR. PHILLIPS: Object to the form.

20 BY THE WITNESS:

21 A. That he would go to John Leiden or both.

22 BY MR. ZWICKER:

23 Q. John Leonard?

24 A. John Leonard. To argue why the study

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1 should continue, to reconfirm our -- our view.

2 Q. That Perry Nisen would do that?

3 A. That's right.

4 Q. That wasn't something you did?

5 A. No, Perry would do that.

6 Q. Dr. Nabulsi, other than instructing Jim
7 Looman and Diane D'Amico to contact the sites in
8 the Netherlands, what other steps did you take to
9 shut down all development activities for ABT-518?

10 MR. PHILLIPS: Object to the form.

11 BY THE WITNESS:

12 A. I did call the team and inform them of
13 the decision.

14 BY MR. ZWICKER:

15 Q. And the reasons for it?

16 A. I needed -- well, the team needs to
17 know. That's the typical practice that the team is
18 to be informed.

19 Q. By "team" you meant the project team?

20 A. Project team, yes.

21 Q. Would that include Lise Loberg?

22 A. I don't recall if --

23 Q. Whoever the members of the project team
24 were?

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1 funding agreement.

2 Q. And you knew that in March 2001?

3 A. I don't know when I knew it or before

4 March, during March or after. But I knew that

5 it -- that 518 was in the -- in the agreement

6 discussion.

7 Q. Did you ever have any discussions with

8 John Leonard or Perry Nisen on the subject of the

9 impact on the Hancock deal of terminating

10 development of 518?

11 A. No.

12 Q. Dr. Nabulsi, there came a time when you

13 learned that the halt on the Phase I clinical trial

14 for 518 had been lifted. Is that true?

15 A. That's right.

16 MR. PHILLIPS: Object to the form. Excuse me.

17 BY MR. ZWICKER:

18 Q. When did you learn that?

19 A. I don't recall the exact date. When I

20 looked at the memo you gave me, this --

21 Q. The chronology?

22 A. The chronology. It has a date in there.

23 MR. PHILLIPS: Just for the record, could you

24 refer to the exhibit number.

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1 MR. ZWICKER: It's 13.

2 MR. PHILLIPS: Thank you.

3 BY THE WITNESS:

4 A. 13, yes.

5 Did I answer or do I need to answer?

6 BY MR. ZWICKER:

7 Q. The question was when you learned that

8 the halt on the clinical trial for ABT-518 had been

9 lifted.

10 A. I'm sorry. Can you repeat that?

11 Q. Yeah. When did you learn that the halt

12 on the clinical trial for ABT-518 had been lifted?

13 MR. PHILLIPS: Object to the form.

14 BY THE WITNESS:

15 A. I learned shortly after the decision to

16 halt.

17 BY MR. ZWICKER:

18 Q. Within a day or two?

19 A. I thought within -- within -- actually

20 within a week or two. But this shows it's within a

21 day or two. Within a day actually.

22 Q. Who told you?

23 A. Perry.

24 Q. What did he tell you?

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1 A. That he discussed the -- our reasoning
2 again with Jeff.

3 Q. Leiden?

4 A. With Jeff Leiden and they were able --
5 and he was able to convince him to restart.

6 Q. Did Dr. Nisen tell you exactly what
7 information he discussed with Dr. Leiden that
8 caused Dr. Leiden to restart the clinical trial?

9 A. I don't recall.

10 Q. Now, sir, in fact, Dr. Leiden didn't
11 agree to recommence all development activities for
12 518 but only the clinical trial. Is that right?

13 A. I don't recall, but it would not have
14 mattered. The reason for that, the clinical trial
15 was the key thing we were doing at the time to get
16 our first clue on the activity or the safety for
17 518. We had significant amount of compound. So,
18 the chemistry part was covered. Any additional
19 preclinical work would not have been necessary to
20 complete the Phase I.

21 Q. My question to you was a little bit
22 different. It is: Isn't it true that Dr. Leiden
23 allowed only the recommencement of the clinical
24 trial but no other development activities with

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1 respect to 518?

2 A. I cannot answer your question as stated

3 because I did not talk to Jeff directly. My

4 recollection is that we are to continue the Phase I

5 to generate data from 518 to be able to convince

6 management, including Jeff, that this product does

7 possess -- does have characteristics to

8 differentiate it from the competition.

9 Q. The development of ABT-518 included more

10 than the clinical trial, correct?

11 A. Correct.

12 Q. Your understanding was that Dr. Leiden

13 had lifted the halt only on the clinical trial,

14 correct?

15 MR. PHILLIPS: Objection; asked and answered.

16 BY THE WITNESS:

17 A. I cannot recall. But as I said, it's

18 not really significant for me at the time, the

19 other activities, because the clinical trial was

20 the key thing I'm looking for.

21 BY MR. ZWICKER:

22 Q. I'm not at this moment asking for your

23 opinion. I'm just asking whether you understood

24 that all development activities except for the

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1 clinical trial would remain on hold.

2 A. I don't recall such an instruction.

3 Q. Do you recall Dr. Leiden instructing

4 that development activities for 518 would remain on

5 hold until May of 2001 when Pfizer would release

6 new data for prinomastat?

7 MR. PHILLIPS: Objection to the form.

8 BY THE WITNESS:

9 A. Again, the question is difficult to

10 answer that way.

11 BY MR. ZWICKER:

12 Q. Do you want me to try to put it to you

13 again?

14 A. Please.

15 Q. Did you learn in March 2001 that

16 Dr. Leiden decided to continue to hold development

17 activities for 518 pending review of information

18 from Pfizer in May of 2001?

19 MR. PHILLIPS: Object to the form.

20 BY THE WITNESS:

21 A. The way it's stated, I would say no.

22 BY MR. ZWICKER:

23 Q. Do you have any knowledge that

24 development activities for 518, the continuation of

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1 development activities for 518 were contingent upon
2 the receipt of positive data from Pfizer in May of
3 2001?

4 MR. PHILLIPS: Object to the form.

5 BY THE WITNESS:

6 A. No. There were two factors to look for.
7 One, we wanted clinical trial data from the
8 Phase I. Two, to watch for the competition, ASCO
9 being a key milestone because that was the upcoming
10 date.

11 So, two things we needed: To look for
12 competition, mainly ASCO, because that's the
13 closest, and to generate data internally.

14 If you look at the memo that Diane
15 created, she was saying that three to six months
16 are going to be key for us in augmenting our
17 argument.

18 Q. But --

19 A. That was Exhibit 10.

20 Q. But you did understand that the decision
21 whether to go ahead with the development of 518
22 would in some way be contingent upon the data
23 received at ASCO in 2001?

24 MR. PHILLIPS: Object to the form.

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1 BY THE WITNESS:

2 A. That it would be -- that the data in

3 ASCO would be important to the future of 518.

4 BY MR. ZWICKER:

5 Q. What did you understand that the ASCO

6 data -- strike that.

7 Did you understand that the ASCO data

8 with respect to the competitors had to be positive

9 in order for 518's development to continue?

10 MR. PHILLIPS: Object to the form.

11 BY THE WITNESS:

12 A. No, not that way.

13 BY MR. ZWICKER:

14 Q. What way?

15 A. That the ASCO data is key for us to be

16 able to maintain the confidence on the compound,

17 but it was not predetermined that ASCO data, if

18 negative, would kill the product.

19 Q. What data were you expecting from ASCO

20 in 2001?

21 A. More competitive data. I don't recall

22 exactly which compound on what study we were

23 waiting for. But there were new data that we were

24 expecting to see. I don't recall the exact

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1 specifics of which pieces of data we were looking
2 for.

3 Q. Now, from the documents we've seen,
4 Abbott had been tracking most closely four
5 compounds. True?

6 MR. PHILLIPS: Object to the form.

7 BY THE WITNESS:

8 A. From the documents we've seen, four
9 compounds were described over and over, yes.

10 BY MR. ZWICKER:

11 Q. Was Abbott anticipating data with
12 respect to one or more of those four compounds?

13 MR. PHILLIPS: Object to the form.

14 BY THE WITNESS:

15 A. We would expect data from those
16 compounds and probably other earlier compounds as
17 well.

18 BY MR. ZWICKER:

19 Q. But none of those other compounds we've
20 seen in the documents so far were being tracked by
21 Abbott, right?

22 MR. PHILLIPS: Object. Objection to the form,
23 mischaracterizes the testimony.

24 BY THE WITNESS:

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1 BY MR. ZWICKER:

2 Q. Well, let me -- let me ask it this way.

3 Did you know in March of 2001 that Dr. Leiden had

4 put all development activities with the exception

5 of the clinical trial on hold?

6 MR. PHILLIPS: Object to the form.

7 BY THE WITNESS:

8 A. I don't recall.

9 BY MR. ZWICKER:

10 Q. You don't recall?

11 A. I don't recall.

12 Q. You would agree with me that as the

13 venture head for 518, that would have been a fact

14 that you would have been very interested in

15 learning, correct?

16 A. Absolutely.

17 (WHEREUPON, a certain document was

18 marked Nabulsi Deposition Exhibit

19 No. 17, for identification, as of

20 01-24-2007.)

21 MR. ZWICKER: The record should reflect that

22 before the witness is Nabulsi Exhibit No. 17, which

23 is a chain of e-mails dated May 25, 2001.

24 BY MR. ZWICKER:

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1 Q. Dr. Nabulsi, could you review

2 Exhibit 17. I realize that you are not cc'd on any

3 of the e-mails here.

4 A. Um-hmm.

5 Okay.

6 Q. Take a look at the earliest e-mail in

7 the chain. It says, "Diane."

8 Pardon the confusion that the sender and

9 recipient are both named Diane.

10 But, "Diane, can Lise proceed with any

11 of the ABT-518 activities that were previously put

12 on halt (i.e., very long chain fatty acid sample

13 analysis from the six-week rat study and histopath

14 from the three-month rat study)?" Signed Diane.

15 And then the response is, "Maybe you

16 read the email below wrong. Can we wait until

17 Diane says Yes/No? I don't want you to start

18 something that is still on hold."

19 Did I read that right?

20 MR. PHILLIPS: I think you skipped the middle

21 e-mail.

22 MR. ZWICKER: The middle one?

23 MR. PHILLIPS: Yeah.

24 MR. ZWICKER: Oh, "Will do." I skipped the

1 "Will do" in the middle.

2 BY THE WITNESS:

3 A. Okay.

4 BY MR. ZWICKER:

5 Q. Dr. Nabulsi, does this refresh your

6 recollection that -- well, strike that.

7 Lise Loberg was the person on the

8 project team who had responsibility for toxicology,

9 correct?

10 A. Yes.

11 Q. And does this refresh your recollection

12 that the toxicology portion of the development

13 activities for ABT-518 were put on hold and the

14 hold was never lifted?

15 MR. PHILLIPS: Objection; compound.

16 BY THE WITNESS:

17 A. This reminded me that we put activities

18 on hold. I cannot tell if hold was never lifted.

19 BY MR. ZWICKER:

20 Q. Well, this -- the date here is May 25,

21 2001. Do you see that?

22 A. That's right.

23 Q. Okay. You testified earlier that in

24 March of 2001 you got the word from Dr. Nisen to

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1 Q. You mean when the study was permanently
2 terminated?

3 A. That's right. So, she could be asking
4 this question after the second stop. I'm not sure
5 when the second stop was.

6 Q. I'll represent to you that it was on or
7 about June 1, 2001.

8 A. The second one?

9 Q. Yeah.

10 A. Yeah. So she's asking about ancillary
11 studies. She is asking about some analyses outside
12 the toxicology study, the main toxicology study.

13 So, I don't recall your question now.

14 Q. Yeah. My question to you is: Does this
15 refresh your recollection that the toxicology
16 component of ABT-518 remained on hold after
17 March 2001?

18 MR. PHILLIPS: Object to the form.

19 BY THE WITNESS:

20 A. See, my difficulty with answering the
21 question is the program already had limited
22 toxicology work. So, the key toxicology work that
23 we needed to proceed with the Phase I was already
24 done. Any additional work that plan was very

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1 limited, was not critical. So that's probably why

2 I don't even remember that.

3 BY MR. ZWICKER:

4 Q. You testified that Dr. Leiden in

5 March halted all development activities for 518,

6 correct?

7 MR. PHILLIPS: Objection; mischaracterizations

8 the testimony.

9 BY THE WITNESS:

10 A. He asked us to stop. That's what I

11 recall.

12 BY MR. ZWICKER:

13 Q. All development activities?

14 A. See, I don't recall the "all development

15 activities."

16 Q. Well, that's what your e-mail to Jim

17 Looman said, correct?

18 A. That's right. But I don't recall what

19 Jeff said. I never had discussions with Jeff.

20 Q. Well, you used the word "all development

21 activities," right?

22 A. That's right, that's correct.

23 Q. Okay. And my question to you is: Isn't

24 it true that toxicology activities for 518

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1 continued to be on hold after the clinical trial

2 halt was lifted?

3 MR. PHILLIPS: Object to the form.

4 BY THE WITNESS:

5 A. I don't want to speculate or guess.

6 BY MR. ZWICKER:

7 Q. I don't want you to.

8 A. Yeah. It's -- any toxicology activity,

9 that would have been -- that would have been -- to

10 be conducted would not have been essential to the

11 program. So, whether I asked for it to stop or not

12 was not really key at the time or whether Jeff

13 asked for it to stop or not wasn't key for the

14 program.

15 Q. Okay. I understand that that's your

16 opinion. My question to you was only: Isn't it

17 true that certain aspects of the development

18 process for 518 remained on hold after March 2001?

19 MR. PHILLIPS: Object to the form.

20 BY THE WITNESS:

21 A. I don't recall -- if I'm going to answer

22 correctly, I can't recall exactly what were the

23 instructions to all parties of the team.

24 BY MR. ZWICKER:

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1 Q. What else?

2 A. I don't recall.

3 Q. Okay. Dr. Nabulsi, isn't it true that
4 before 518 was eventually terminated Abbott never
5 finished the Phase I trial either, did it?

6 A. Before -- can you repeat, please?

7 Q. Yes. Isn't it true that before ABT-518
8 was finally terminated in June of '01, Abbott had
9 never finished the Phase I clinical trial?

10 MR. PHILLIPS: Object to the form.

11 BY THE WITNESS:

12 A. The study was not completed.

13 MR. ZWICKER: 18.

14 (WHEREUPON, a certain document was
15 marked Nabulsi Deposition Exhibit
16 No. 18, for identification, as of
17 01-24-2007.)

18 BY MR. ZWICKER:

19 Q. Dr. Nabulsi, as of March 13, 2001, is it
20 fair to say that your understanding of the
21 development status of 518 was as follows: First,
22 that Abbott would have to await the results of
23 additional competitor data. True?

24 MR. PHILLIPS: Objection; vague. I'm sorry.

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1 Objection to the form.

2 BY THE WITNESS:

3 A. You said Abbott have to wait. I'm not
4 sure have to wait.

5 BY MR. ZWICKER:

6 Q. As of March 13, 2001, is it fair to say
7 that the continued development of ABT-518 was
8 dependent upon the results of competitor data at
9 the ASCO conference in 2001? Is that true?

10 MR. PHILLIPS: Objection to the form.

11 BY THE WITNESS:

12 A. That ASCO competitor data crucial for
13 518 future. That was my understanding.

14 BY MR. ZWICKER:

15 Q. Take a look at what has been put before
16 you as Exhibit 18, which is a descriptive
17 memorandum from February 2001.

18 Have you ever seen this document before?

19 A. Yesterday.

20 Q. That's the first time?

21 A. Sure. However, this would have been
22 prepared by my team.

23 Q. And by "this" you mean the very last
24 page?

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1 MR. PHILLIPS: I'm sorry. Objection to the
2 form; incomplete hypothetical.

3 BY THE WITNESS:

4 A. Can you repeat?

5 BY MR. ZWICKER:

6 Q. Sure.

7 A. I'm not sure how to answer that, yeah.

8 Q. Dr. Nabulsi, would you have personally
9 wanted to know if you were investing in ABT-518
10 that Abbott had discontinued all development
11 activities in March of 2001 because of bad
12 competitor data?

13 MR. PHILLIPS: Objection; mischaracterizes the
14 testimony. Object to the form, incomplete
15 hypothetical.

16 BY THE WITNESS:

17 A. If I'm investing in 518, I would like to
18 know what was the status of 518.

19 BY MR. ZWICKER:

20 Q. You would have liked to have that
21 information?

22 A. I would have liked to have information
23 on 518. I mean, as an investment interest, I would
24 like to know what's going on.

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1 Q. Your understanding was that Dr. Leiden
2 anticipated seeing additional data at ASCO in
3 May 2001, correct?

4 A. That's right.

5 Q. Was Dr. Leiden hopeful that he would see
6 good data in order to continue the development of
7 ABT-518?

8 MR. PHILLIPS: Object to the form.

9 BY THE WITNESS:

10 A. I can answer the first part. I believe
11 Dr. Leiden wanted to see good data.

12 I cannot answer the second part of the
13 question, in order to continue, because he never
14 communicated that to me.

15 Q. Okay. Do you recall having any
16 conversations with anyone at Abbott regarding the
17 discontinuance of ABT-518 in connection with the
18 Hancock deal?

19 A. No.

20 Q. None. At some point you directed your
21 staff to inform the sites that the hold on the
22 clinical trial had been lifted, right?

23 A. Yes.

24 Q. Who did you ask to do that?

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1 A. I don't recall exactly, but the typical
2 practice would have been the senior project
3 manager, which is in this case Diane, and the
4 operation manager, which if I recall correctly was
5 Bob Hansen.

6 Q. Dr. Nabulsi, do you recall any
7 resistance from the sites in restarting the
8 clinical trial?

9 A. They were -- they were concerned that we
10 are committed.

11 Q. What do you mean?

12 A. Because we stopped due to prioritization
13 of portfolio and the competition and then we said
14 we need to start again, and the question was, "Are
15 you committed to continue?"

16 Q. What did you -- what did you or your
17 designee tell the sites about the reasons why the
18 halt on the study had been lifted?

19 MR. PHILLIPS: Object to the form.

20 BY THE WITNESS:

21 A. Our discussion was, as internal and
22 external, that we believe we still have a better
23 compound than the competition and we need the data
24 from Phase I to be able to at least confirm if this

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1 drug has some of the characteristics we're looking
2 for to go to the next stage.

3 So, they -- we believed in that. We --
4 that was our internal position and we basically
5 talked -- told them that this is our agreement with
6 management, that we need to continue the Phase I to
7 be able to characterize the compound better and
8 make a more informed go/no go.

9 BY MR. ZWICKER:

10 Q. What additional assurances were the
11 sites looking for to test Abbott's commitment to
12 seeing the clinical trial through to completion?

13 MR. PHILLIPS: Object to the form.

14 BY THE WITNESS:

15 A. The primary thing is more personal
16 relationship and commitments.

17 BY MR. ZWICKER:

18 Q. How did you mean?

19 A. We knew these investigators. We worked
20 with them as advisers as well. Some of them worked
21 on other studies in the past for us. So, there is
22 a relationship and trust with myself and other
23 members of my staff.

24 So, the assurance, we said we have a go

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1 probabilities will multiply together and give you

2 an overall probability of success to launch.

3 BY MR. ZWICKER:

4 Q. Fair to say that in Abbott's oncology

5 program as of March 2001 that ABT-518 stood the

6 lowest probability of launch in the group?

7 A. Based on this table you are showing me,

8 it has the lowest number, yeah.

9 Q. So, that means it had the lowest

10 probability of launch, correct?

11 A. Correct.

12 (WHEREUPON, a certain document was

13 marked Nabulsi Deposition Exhibit

14 No. 21, for identification, as of

15 01-24-2007.)

16 MR. ZWICKER: The record should reflect that

17 before the witness is Nabulsi Exhibit No. 21, which

18 are MMPI monthly meeting agendas and notes.

19 BY MR. ZWICKER:

20 Q. Dr. Nabulsi, do you recognize this

21 document?

22 A. The type of document, yes.

23 Q. Do you have any recollection of

24 attending project team meeting on the 12th of

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 Q. Dr. Nabulsi, in April of 2001, was it
2 your personal view that Dr. Leiden was pessimistic
3 about the prospects of ABT-518?

4 A. Yes.

5 Q. Is it your view that Dr. Leiden was more
6 likely than not to terminate the compound?

7 MR. PHILLIPS: Are you asking was it his view
8 at the time?

9 MR. ZWICKER: Yes.

10 BY THE WITNESS:

11 A. There were high risk that he would
12 terminate the program.

13 BY MR. ZWICKER:

14 Q. And did you have that view on March the
15 13th when Dr. Leiden permitted the clinical study
16 to continue?

17 A. No.

18 Q. You had a different view?

19 A. That's right.

20 Q. What was your view then?

21 A. My view that he allowed us to continue
22 based on the discussion with Perry to be able to
23 demonstrate in the Phase I whether the compound has
24 some of the characteristics we're looking for to

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1 show that it is -- to confirm our argument that it
2 is better than the competition, our argument in
3 relation to selectivity, our argument in relation
4 to the potency against MMPIs, specificity against
5 MMPIs and so on.

6 Q. Well, I understand your testimony
7 that --

8 MR. PHILLIPS: I'm sorry. Were you finished
9 with your response?

10 THE WITNESS: No, not yet.

11 BY MR. ZWICKER:

12 Q. Okay. Go ahead.

13 A. So, we wanted -- we understood that we
14 need -- we have a shot to get results from the
15 Phase I to be able to show him that we have -- we
16 have no joint toxicity. If so, that will confirm
17 our argument to proceed forward, knowing that the
18 ASCO meeting is a crucial meeting for us.

19 Q. Okay.

20 A. And that's how I proceeded.

21 Q. All right. But in March 2001 was your
22 personal view that the odds were stacked against
23 you regarding the development of ABT-518?

24 MR. PHILLIPS: Object to the form; asked and

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1 answered.

2 BY THE WITNESS:

3 A. We knew due to the competition that we
4 have tough argument to make, but we believed in
5 that argument based on the selectivity and -- and
6 the profile of 518 compared to the competition.

7 But we had to convince management,
8 convince outside consultant of that argument, which
9 we believe we had a lot of internal and external
10 folks who believed in that argument as well.

11 BY MR. ZWICKER:

12 Q. In March 2001, with respect to
13 Dr. Leiden anyway, you personally believed that you
14 had an uphill climb, didn't you?

15 MR. PHILLIPS: Objection; asked and answered.

16 BY THE WITNESS:

17 A. Because of the events, yes. We were
18 concerned that he needed more information, more --
19 more -- more convincing along the way.

20 BY MR. ZWICKER:

21 Q. And isn't it true that in March 2001 you
22 were not optimistic that you were going to get
23 favorable data at the ASCO conference in May?

24 MR. PHILLIPS: Objection to the form.

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1 BY THE WITNESS:

2 A. I would not say that. I would not have

3 restarted the study if I was so pessimistic.

4 BY MR. ZWICKER:

5 Q. But you had no indication that the data

6 you'd get in May was going to be favorable, did

7 you?

8 MR. PHILLIPS: Objection to form.

9 BY THE WITNESS:

10 A. Favorable as to what?

11 BY MR. ZWICKER:

12 Q. As to the competitors?

13 MR. PHILLIPS: Object to the form.

14 BY THE WITNESS:

15 A. Depending on how you define "favorable"

16 because data -- you know, my view was always that

17 the data can have two edges. One is to tell you if

18 the drug -- if other drugs work, which -- which

19 will tell you about the class and the confidence in

20 the class. But at the same time, will tell you

21 maybe if you have a winner, you could really own

22 the market and have a strong -- a strong drug.

23 So, you know, I always looked at the

24 two -- at the two views. Every piece of data

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1 affected the balance.

2 Q. Okay. You were not confident that you
3 were going to see a competitor in May 2001 whose
4 compound did not demonstrate joint toxicity, right?

5 MR. PHILLIPS: Objection to the form.

6 BY THE WITNESS:

7 A. Can you repeat?

8 BY MR. ZWICKER:

9 Q. Yeah. In March, you didn't have
10 confidence that any of the MMPI competitors would
11 fail to demonstrate joint toxicity, right?

12 A. Did not -- I'm trying to restructure
13 your statement.

14 Q. Let me ask it again.

15 A. It's difficult to answer yes or no to
16 it.

17 Q. Let me ask it again.

18 In March 2001 you felt pretty sure that
19 your competitors were all going to demonstrate
20 joint toxicity, right?

21 A. No, not really because Bayer already
22 demonstrated no joint toxicity. So, there is a
23 chance others will demonstrate no joint toxicity.

24 Q. But of the four you were tracking, all

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1 three of them had demonstrated joint toxicity --

2 A. That's right.

3 Q. -- correct?

4 A. That's right.

5 MR. PHILLIPS: Objection. I'm sorry, but the

6 question made no sense. Of the four you were

7 tracking, all three of them demonstrated -- I'm

8 sorry. Objection.

9 BY MR. ZWICKER:

10 Q. Of the four you were tracking, with the

11 exception of Bayer, all three demonstrated joint

12 toxicity, right?

13 A. Correct. That was, for me personally,

14 that was not a bad thing because with the research

15 team we were very comfortable that the hypothesis

16 of gelatinase and the selectivity could work for us

17 in relation to the joint toxicity issue.

18 Q. But, in fairness, you hadn't convinced

19 Dr. Leiden of that. True?

20 MR. PHILLIPS: Objection to the form.

21 BY THE WITNESS:

22 A. But that's not the only -- not the only

23 factor in any consideration. Efficacy was one.

24 Other factors. Portfolio was another one.

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1 MR. PHILLIPS: Object to the form.

2 BY THE WITNESS:

3 A. There were no absolute conclusion at the
4 time that results in ASCO would -- would conclude
5 killing the product.

6 BY MR. ZWICKER:

7 Q. Turn to the first page of the document
8 we have in front of you. Do you see in handwriting
9 it says, "Per Perry: Kill scenario"?

10 A. Correct.

11 Q. "Leiden wants to make go/no go decision
12 based on competitor data at ASCO: Committed."

13 Do you see that?

14 A. Yes.

15 Q. Was that your understanding, that
16 Dr. Leiden was going to make the decision whether
17 or not to terminate ABT-518 based on what he saw at
18 ASCO?

19 A. As I said, ASCO was a very crucial
20 meeting for us. So, the risk was high that based
21 on the ASCO we'll have a decision from Jeff Leiden.
22 But that was not -- there were no communication to
23 me if negative, it's a kill.

24 Q. Communications to you?

1 BY MR. ZWICKER:

2 Q. Dr. Nabulsi, if you could, turn to

3 page 3 of 6.

4 A. 3 of 3?

5 Q. 3 of 6.

6 A. Numbered wrong.

7 MR. PHILLIPS: I think we have a different --

8 MR. ZWICKER: We have a different pagination?

9 MR. PHILLIPS: Well, I don't know. Ours says

10 3 of 3 on the page.

11 MR. ZWICKER: Oh, I see. Let me give you the

12 Bates number.

13 BY THE WITNESS:

14 A. It's a different document.

15 BY MR. ZWICKER:

16 Q. It's a different document. Okay. Hold

17 on to those for a second.

18 MR. ZWICKER: This is the one that should be

19 marked -- maybe you --

20 MR. PHILLIPS: We want to dispose of this one?

21 MR. ZWICKER: Why don't we mark this 24 and

22 put this one aside.

23 (WHEREUPON, a certain document was

24 marked Nabulsi Deposition Exhibit

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 No. 24, for identification, as of

2 01-24-2007.)

3 MR. PHILLIPS: This is 24. And you wanted him

4 to go to 3 of 3.

5 MR. ZWICKER: Page 3 of 6 and read the

6 paragraphs marked "Strategy/" Process --

7 "Progress."

8 BY THE WITNESS:

9 A. Okay.

10 BY MR. ZWICKER:

11 Q. Okay. Dr. Nabulsi, does this help you

12 remember that in early May of 2001 Abbott received

13 data that marimastat patients with gastric cancer

14 were more likely to be alive than those who had

15 received placebo in clinical trials?

16 A. Yes.

17 Q. And did Abbott view this development as

18 a favorable development for 518?

19 MR. PHILLIPS: Objection to the form.

20 BY THE WITNESS:

21 A. Was -- was positive. You have both

22 views in the same statement. But overall, at least

23 on my side and the clinical team side, we were

24 still optimistic to continue, yeah.

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1 BY MR. ZWICKER:

2 Q. But you viewed the development for

3 marimastat as a positive development?

4 A. Yes.

5 Q. And if you look at the very bottom of

6 the page there is some news about BMS, which is the

7 Bristol-Myers Squibb drug?

8 A. Yes.

9 Q. Do you see that?

10 A. Yes.

11 Q. And Abbott learned that BMS was starting

12 Phase II trials in non-small cell lung cancer and

13 Kaposi's. Do you see that?

14 A. Yes.

15 Q. At that time you didn't have the results

16 of the Phase II trials for BMS. True?

17 A. That's right. They were just starting.

18 Q. Did you attend the ASCO conference in

19 2001?

20 A. I don't recall the exact conference, but

21 my practice was to attend those meetings.

22 Q. Do you recall attending the conference

23 with anyone else?

24 A. Do you recall when -- where was that

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 conference?

2 Q. None of the documents I have tell me.

3 A. The general practice was that I go to
4 these conferences. My team, my clinical team, will
5 go to the conferences. We look at new data. We
6 meet with investigators, with advisers as well.

7 Q. Do you recall whether Todd Janus
8 attended the conference with you?

9 A. Todd typically -- general practice was
10 that Todd will attend those meetings as well. I
11 don't recall vividly, you know, me standing there
12 with Todd.

13 Q. Who else other than you and Todd would
14 attend ASCO meetings?

15 A. Myself, Todd, Perry, research
16 colleagues, Diane D'Amico, Bob Hansen. Most of the
17 team will attend, at least from Diane D'Amico level
18 and higher, would attend those conferences.

19 Q. Do you take notes at the ASCO
20 conference?

21 A. I -- I rarely do.

22 Q. Rarely?

23 A. Yeah.

24 Q. Is someone charged with taking notes at

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 ASCO?

2 A. That's right. Like Diane, Bob, research

3 colleague takes a lot of notes. That's typical

4 practice.

5 Q. What about handouts, abstracts and such?

6 A. If they -- they would pull abstracts. I

7 would pull abstracts, too, from -- from the

8 meeting. There is a book usually as well. So,

9 there is a book that gets distributed to those who

10 attend the meeting, has abstracts.

11 But also with the posters, which I

12 described to you earlier the posters, most of the

13 posters -- almost all the poster presenters will

14 give you a copy of their poster.

15 Q. What does the -- what information does

16 the poster contain?

17 MR. PHILLIPS: Object to the form.

18 BY THE WITNESS:

19 A. A poster will contain experiment

20 information, whether clinical trial or preclinical

21 experiment, objectives, methods, results,

22 conclusions.

23 BY MR. ZWICKER:

24 Q. And you would agree with me that some of

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1 the data available at ASCO has previously been made
2 available through public sources, correct?

3 MR. PHILLIPS: Object to the form.

4 BY THE WITNESS:

5 A. They -- there is a book that's
6 distributed that has some data, but the details of
7 the data usually given the day of the presentation
8 or the day when the poster is presented.

9 BY MR. ZWICKER:

10 Q. My question is there is some data that
11 is presented at ASCO that was already made
12 available by pharmaceutical companies in the public
13 domain?

14 MR. PHILLIPS: Objection; asked and answered.

15 BY THE WITNESS:

16 A. Not to the same details.

17 BY MR. ZWICKER:

18 Q. But generally speaking?

19 MR. PHILLIPS: Same -- object to the form.

20 BY THE WITNESS:

21 A. It's difficult to answer because
22 sometimes you cannot release information before the
23 meeting if it is new, significant information.
24 They don't allow companies or researchers to

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1 publicly announce before the meeting.

2 BY MR. ZWICKER:

3 Q. But as we discussed, Abbott is --

4 monitors public databases for information relating

5 to its competitors. True?

6 A. Correct.

7 MR. ZWICKER: Let's mark this as the next

8 exhibit.

9 (WHEREUPON, a certain document was

10 marked Nabulsi Deposition Exhibit

11 No. 25, for identification, as of

12 01-24-2007.)

13 MR. ZWICKER: Before the witness is

14 Exhibit 25, which is an e-mail from Perry Nisen to

15 Azmi Nabulsi dated May the 20th, 2001.

16 BY MR. ZWICKER:

17 Q. Do you recognize this document?

18 A. Yes.

19 Q. What do you recall about Perry Nisen's

20 request to you regarding ASCO?

21 A. Let me just read that now.

22 Yeah, I believe this was to communicate

23 with John Leonard and then Jeff about the ASCO

24 meetings, the outcome of the ASCO meetings and our

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1 recommendations beyond the ASCO -- based on -- on
2 the ASCO meetings as a follow-up to the March --
3 the March discussions, March.

4 Q. Do you know -- do you know why Dr. Nisen
5 asked you to prepare the slides?

6 MR. PHILLIPS: Object to the form.

7 BY THE WITNESS:

8 A. Why -- why -- what's the purpose or why
9 me?

10 BY MR. ZWICKER:

11 Q. No. Why was the request directed to
12 you, do you know?

13 A. Because I'm heading the program. I'm
14 responsible for the development of the...

15 Q. Does the fact that Dr. Nisen asked you
16 to summarize the ASCO program help you remember
17 that you were present for it?

18 A. Yes, as I said, as a general practice I
19 attended those meetings. I don't remember vividly,
20 you know, walking in the hallways and looking at
21 the data and so on.

22 Q. And did you, in fact, prepare slides for
23 Dr. Leonard and Dr. Leiden?

24 A. I believe so.

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1 Q. How did you do that?

2 A. I would typically ask my team to pull

3 the information from ASCO. As a general practice

4 actually. Not only for that. All the competitive

5 information they gather, to pull it together, put

6 it in a set of slides and give it to me.

7 We usually as a general practice had

8 those discussed at the next project meeting. But

9 in this case, obviously, this was requested for a

10 different purpose.

11 Q. And is it fair to say that the slides

12 that your group collected reflected the most

13 important information for Abbott regarding the ASCO

14 conference?

15 MR. PHILLIPS: Object to the form.

16 BY THE WITNESS:

17 A. They would summarize the most important

18 information.

19 (WHEREUPON, a certain document was

20 marked Nabulsi Deposition Exhibit

21 No. 26, for identification, as of

22 01-24-2007.)

23 MR. ZWICKER: Before the witness is Nabulsi

24 Exhibit No. 26, which is a series of slides that

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

- 1 begins with the slide entitled "ASCO 2001 MMPI
- 2 Update."
- 3 BY MR. ZWICKER:
- 4 Q. Dr. Nabulsi, do you recognize
- 5 Exhibit No. 26?
- 6 A. Yes.
- 7 Q. Are these the slides that you caused to
- 8 be prepared at the direction of Dr. Nisen?
- 9 A. I believe so. They look -- they look
- 10 direct answer to his question, yes.
- 11 Q. You reviewed these slides before they
- 12 were provided to Dr. Nisen?
- 13 A. I'm sure I did.
- 14 Q. You reviewed them for completion and
- 15 accuracy?
- 16 A. Correct.
- 17 Q. Now, you say at the very top of the
- 18 first slide, "Ten MMPI abstracts were presented."
- 19 Do you see that?
- 20 A. Yes.
- 21 Q. And then you go on to summarize the
- 22 results of only four of those abstracts, right?
- 23 A. Well, I don't know if they are four
- 24 abstracts because ten abstracts, but they could

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1 MMPI abstracts were reflecting four compounds or
2 the four compounds were the most important
3 compounds to be addressed.

4 Q. You say in the first slide that
5 prinomastat, marimastat and the Bayer drug reported
6 negative findings, right?

7 A. Right.

8 Q. But then you go on to try to provide
9 explanations for those negative findings, correct?

10 A. Correct.

11 Q. And is your purpose in providing
12 explanations to distinguish 518 from the other
13 compounds?

14 A. Correct. This has been the -- our
15 rationale from earlier communications you've seen
16 on differentiating 518 from the competitors.

17 Q. Let's turn the page to the prinomastat
18 slide. And I think it would be helpful for us to
19 have several exhibits in front of you.

20 If you could put in front of you
21 Exhibit No. 3.

22 A. No. 3?

23 Q. Um-hmm. Exhibit No. 6 and
24 Exhibit No. 23.

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1 A. -- piece of data has been known before.

2 Q. Take a look at Exhibit 3, page 3.

3 The second full paragraph, two-thirds of
4 the way down the page, reads, "Pfizer announced on
5 8/4/2000 that Phase III clinical trials of
6 prinomastat in patients with advanced non-small
7 cell lung cancer (in combination with
8 paclitaxel/carboplatin and with
9 gemcitabine/cisplatin) and in advanced
10 hormone-refractory prostate cancer have been
11 discontinued. The reason given was 'primary
12 efficacy objectives were not met.'"

13 Do you see that?

14 A. Yes, for prostate cancer.

15 Q. And for lung cancer?

16 A. Yes.

17 Q. So, it's true that Abbott knew before
18 ASCO that prinomastat had demonstrated no survival
19 benefit in lung cancer, right?

20 A. Correct.

21 Q. Look at the next bullet point on the
22 ASCO slides, which is Exhibit 26, which is,
23 "Hormone refractory prostate cancer."

24 Do you see that?

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1 A. Yes.

2 Q. Also true that Abbott knew before ASCO
3 that prinomastat demonstrated no survival benefit
4 for hormone refractory prostate cancer?

5 MR. PHILLIPS: Objection to the form.

6 BY THE WITNESS:

7 A. I'm not sure if this is the same study.

8 This is in combination with mitoxantrone and
9 prednisone. So, it's difficult to tell if the
10 prostate statement here is the same.

11 BY MR. ZWICKER:

12 Q. Well, let's go back to Exhibit 3 and
13 that same sentence we read before.

14 At the risk of once again butchering
15 these pronunciations, "Pfizer announced on 8/4/2000
16 that Phase III clinical trials of prinomastat
17 patients with," and I'm skipping down, "advanced
18 hormone-refractory prostate cancer patients in
19 combination with mitoxantrone/prednisone have been
20 discontinued. The reason given was 'primary
21 efficacy objectives were not met.'"

22 A. Correct. So, in -- that was
23 communicated then, yes.

24 Q. Okay. And then the next bullet point

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1 with respect to prinomastat is "Refractory

2 metastatic" -- "metastatic breast cancer."

3 Do you see that?

4 A. Yes.

5 Q. And from your slide it appears that

6 there was no significant data one way or another

7 with respect to prinomastat and treatment of breast

8 cancer, right?

9 MR. PHILLIPS: Object to the form.

10 BY THE WITNESS:

11 A. We just say that there is -- there is a

12 study ongoing. There is nothing, no data.

13 Q. Next bullet point for prinomastat is,

14 "Grade 2 joint toxicity in above trials at all dose

15 levels (5, 10, 25 mgs bid)."

16 Do you see that?

17 A. Yes.

18 Q. And Abbott was aware before ASCO that

19 prinomastat demonstrated joint toxicity?

20 A. Correct.

21 MR. PHILLIPS: Object to the form.

22 BY MR. ZWICKER:

23 Q. And then the last bullet point is,

24 "Studies in earlier stage tumors are still

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 ongoing." Do you see that?

2 A. Yes, I see that.

3 Q. And, so, you would conclude that

4 Abbott -- that there was no additional data

5 available regarding additional studies for early

6 stage tumors?

7 MR. PHILLIPS: Objection to the form.

8 MR. ZWICKER: Let me ask.

9 BY THE WITNESS:

10 A. There may be no additional conclusions,

11 but there may have been new data.

12 BY MR. ZWICKER:

13 Q. But you're not summarizing any new data

14 regarding additional studies in early stage tumors

15 as a result of ASCO?

16 A. That's right, but there could have been

17 more -- more information supporting these

18 conclusions here. But I'm not -- but they're not

19 in the summary, yes.

20 Q. Right. None that you deemed important

21 enough to summarize, right?

22 MR. PHILLIPS: Objection to the form.

23 BY THE WITNESS:

24 A. I can't tell exactly what was seen. I

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 Q. And your summary does not report any key
2 findings one way or another with respect to
3 treatment of glioblastoma, right?

4 MR. PHILLIPS: Objection to the form.

5 BY MR. ZWICKER:

6 Q. Is that true?

7 A. That's reporting that there is -- that's
8 right. There is no data. There is no results
9 here.

10 Q. And then the final bullet point is,
11 "High dropout rate due to toxicity."

12 Do you see that?

13 A. I see that.

14 Q. And Abbott knew before ASCO that there
15 was joint toxicity with respect to marimastat.
16 True?

17 MR. PHILLIPS: Object to the form.

18 BY THE WITNESS:

19 A. Let me just confirm. I believe so,
20 but --

21 BY MR. ZWICKER:

22 Q. You can look at Nabulsi Exhibit No. 6,
23 page 3 of 3.

24 A. Okay.

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 Q. So, you would agree with me that Abbott

2 knew before ASCO that --

3 A. Yes.

4 Q. -- marimastat patients demonstrated a

5 high dropout rate due to joint toxicity, correct?

6 MR. PHILLIPS: Object to the form.

7 BY THE WITNESS:

8 A. We knew before ASCO that there were

9 joint toxicity with marimastat. But I don't know

10 about the high dropout rate.

11 BY MR. ZWICKER:

12 Q. Okay. Turn the page to tanomastat or

13 BAY 12-9566. Prior to ASCO, Abbott knew that Bayer

14 had terminated the BAY 12-9566 compound, correct?

15 A. Let me refresh my memory here.

16 Q. Take a look at Exhibit 2, page 5.

17 A. Okay. It's described in -- in

18 Exhibit 2.

19 Q. Correct.

20 A. But this is also May. So I'm not sure

21 if that was the first time we learned in May or

22 not.

23 Q. In any event, as of ASCO, which is in

24 May of 2001, Abbott knows that Bayer terminated its

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 A. Yes.

2 Q. So, as of March 2000 Abbott knew that

3 Bayer had withdrawn its drug. True?

4 MR. PHILLIPS: Objection to the form.

5 BY THE WITNESS:

6 A. Based on this document there was a -- we

7 knew that Bayer was withdrawn.

8 BY MR. ZWICKER:

9 Q. So, as of ASCO, which was in May 2000,

10 Abbott was also aware that Bayer had withdrawn --

11 MR. PHILLIPS: Objection.

12 BY MR. ZWICKER:

13 Q. -- its compound?

14 MR. PHILLIPS: Objection to the form. I think

15 you misstated it, counsel, regarding the date of

16 ASCO.

17 BY THE WITNESS:

18 A. 2001.

19 BY MR. ZWICKER:

20 Q. 2001. Let me restate.

21 So, as of May 2001 Abbott knew that

22 Bayer had withdrawn its MMPI candidate. True?

23 A. True.

24 Q. Turn the page to the BMS 275291 drug.

1 MR. PHILLIPS: Objection. Objection to the

2 form.

3 BY MR. ZWICKER:

4 Q. Should I restate it?

5 A. Yeah.

6 Q. Would you agree with me that the results

7 at ASCO were not conclusive in your mind regarding

8 whether development of ABT-518 should continue or

9 stop?

10 A. In my mind ASCO results were not

11 definitive either way. It did not bring

12 significantly new information as far as I was

13 concerned at the time.

14 Q. And you would never say that ASCO

15 resulted in an avalanche of bad data that made the

16 decision to terminate ABT-518 an obvious one,

17 correct?

18 MR. PHILLIPS: Object to the form.

19 BY THE WITNESS:

20 A. It's complicated.

21 BY MR. ZWICKER:

22 Q. Let me state it again.

23 You would agree with me that ASCO did

24 not present a substantial amount of bad data for

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 518, right?

2 MR. PHILLIPS: Object to the form.

3 BY THE WITNESS:

4 A. I did not come out of ASCO -- based on
5 the information I have seen here to refresh my
6 memory, I did not come out of ASCO thinking we
7 should stop 518.

8 BY MR. ZWICKER:

9 Q. In your mind ASCO had some favorable
10 data. True?

11 MR. PHILLIPS: Object to the form.

12 BY THE WITNESS:

13 A. In my mind ASCO had -- did not bring any
14 significant new information.

15 BY MR. ZWICKER:

16 Q. Go back to your -- your slide
17 presentation. At the very back there's a slide
18 called "Recommendations."

19 MR. PHILLIPS: Are you on page 7, counsel?

20 MR. ZWICKER: I am. Thank you, Mr. Phillips.

21 BY MR. ZWICKER:

22 Q. Do the recommendations on page 7 reflect
23 your recommendations and those of the project team
24 regarding ABT-518?

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 yes.

2 Q. So, these are your views in fact?

3 A. Yes.

4 Q. And are these the views of the project
5 team?

6 A. Yes.

7 MR. PHILLIPS: Well, object to the form.

8 Dr. Nabulsi, again, if you could just
9 give me a moment.

10 THE WITNESS: Okay.

11 MR. PHILLIPS: So if I need to interpose an
12 objection, I can.

13 Counsel, I don't mean to interrupt the
14 flow. But when you get to a short break fairly
15 soon, I'd appreciate it.

16 MR. ZWICKER: Why don't we -- how about like
17 in five minutes. Is that okay?

18 MR. PHILLIPS: Sure.

19 (WHEREUPON, a certain document was
20 marked Nabulsi Deposition Exhibit
21 No. 27, for identification, as of
22 01-24-2007.)

23 MR. ZWICKER: The record should reflect that
24 before the witness are a series of documents

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 produced by Abbott containing Bates Nos. 556

2 through -- 556321 through 556349.

3 BY MR. ZWICKER:

4 Q. Dr. Nabulsi, let me just direct your

5 attention to the page Bates numbered ABBT 556334,

6 which is a series of pages beginning with

7 handwriting.

8 A. Okay.

9 Q. Is this your handwriting?

10 A. No.

11 Q. Do you recognize it?

12 A. No.

13 MR. ZWICKER: Why don't we take a break.

14 MR. PHILLIPS: Okay. Great.

15 THE VIDEOGRAPHER: Going off the record. The

16 time now is 4:14 p.m. This is the conclusion of

17 Videotape No. 5.

18 (WHEREUPON, a recess was had

19 from 4:14 to 4:26 p.m.)

20 THE VIDEOGRAPHER: We're back on the record.

21 The time now is 4:26 p.m. This is the beginning of

22 Videotape No. 6.

23 BY MR. ZWICKER:

24 Q. Dr. Nabulsi, did there come a time when

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 you learned that the development of ABT-518 had
2 been terminated?

3 A. Yes.

4 Q. When?

5 A. I don't recall the exact date, but could
6 have been May, June date.

7 Q. Who told you?

8 A. Perry.

9 Q. Who was present when he told you?

10 A. I don't recall.

11 Q. Were you alone?

12 A. I don't recall.

13 Q. How did he tell you, by phone, by
14 e-mail, by meeting?

15 A. I don't recall the exact event. But
16 Perry and I talked face to face a lot. So...

17 Q. What were the reasons he gave you
18 regarding why development of ABT-518 had been
19 terminated?

20 A. I don't recall the exact setting that he
21 told me or the exact words that he told me.

22 Q. What do you recall generally?

23 A. That the competitive data is not
24 supportive to continue and the portfolio

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 prioritization, the same logic from March.

2 Q. Did Dr. Nisen tell you that the decision

3 had been made by Dr. Leiden? By "decision" I mean

4 the decision to terminate ABT-518.

5 A. Yes.

6 Q. He told you that?

7 A. It was made by Leiden, yes.

8 Q. According to Dr. Nisen, what did

9 Dr. Leiden say about the competitive data?

10 A. I don't recall any specifics.

11 Q. Did you believe that you were -- you and

12 the project team were required by Dr. Leiden to

13 demonstrate very positive competitor data at ASCO

14 and that you had failed to do it? Was that your

15 personal view?

16 MR. PHILLIPS: I'm sorry. Objection to the

17 form.

18 BY THE WITNESS:

19 A. No.

20 BY MR. ZWICKER:

21 Q. In your own mind what was it about the

22 competitor data at ASCO that caused the termination

23 of ABT-518?

24 MR. PHILLIPS: Objection; calls for

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 speculation -- well, objection; calls for

2 speculation. Object to the form.

3 BY THE WITNESS:

4 A. I don't know.

5 BY MR. ZWICKER:

6 Q. Sitting here today do you have any

7 recollection of the kind of data you were hoping

8 for from ASCO?

9 A. I was hoping for?

10 Q. Yes.

11 A. No. I mean, my conclusion from the data

12 was in the statement -- in the presentation you've

13 seen.

14 Q. So, in your mind, the ASCO data was

15 neutral?

16 MR. PHILLIPS: Objection to the form.

17 BY THE WITNESS:

18 A. ASCO data did not bring significant new

19 information to the table.

20 Now, I admit I have not seen the

21 specifics of the abstract to recollect -- to

22 refresh my memory, but I don't recall any specific

23 significant information.

24 BY MR. ZWICKER:

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 Q. Did you have an understanding what
2 process was employed by Dr. Leiden to terminate
3 development of ABT-518?

4 MR. PHILLIPS: Objection to the form.

5 BY THE WITNESS:

6 A. No.

7 BY MR. ZWICKER:

8 Q. Did you understand there was a PEC
9 meeting?

10 A. There were monthly meetings. So I can't
11 recall the relation of the decision to a PEC
12 meeting.

13 Q. So, the sole source of your information
14 regarding the reasons for termination of ABT-518
15 came from Dr. Nisen?

16 A. Yes.

17 Q. And you were disappointed in that
18 result?

19 A. I was disappointed in that direction,
20 yes.

21 Q. In your view -- strike that.

22 At the time Dr. Leiden terminated the
23 development of ABT-518, the Phase 1 clinical trial
24 was still underway, correct?

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 A. Correct.

2 Q. So, it's fair to say that the results of
3 the Phase I clinical trial had no impact on the
4 decision to terminate ABT-518?

5 MR. PHILLIPS: Objection to the form.

6 BY THE WITNESS:

7 A. We did not have any results at the time.

8 BY MR. ZWICKER:

9 Q. So, the trial could not have played any
10 role in the decision. Fair?

11 MR. PHILLIPS: Objection to the form. You're
12 talking about the results of the trial?

13 MR. ZWICKER: Correct.

14 BY THE WITNESS:

15 A. Yeah, correct, non-existent.

16 BY MR. ZWICKER:

17 Q. Did you inform the clinical sites of
18 Dr. Leiden's decision?

19 MR. PHILLIPS: Dr. Nabulsi personally?

20 MR. ZWICKER: Yes.

21 BY THE WITNESS:

22 A. Well, I informed them through Jim
23 initially.

24 BY MR. ZWICKER:

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 Q. Jim Looman?

2 A. That's right.

3 Q. Your response to Ms. D'Amico is to
4 direct her not to communicate with the sites yet.
5 Do you see that?

6 A. That's right.

7 Q. Why did you want her to delay?

8 MR. PHILLIPS: Objection to the form.

9 BY THE WITNESS:

10 A. I don't recall.

11 BY MR. ZWICKER:

12 Q. Did you want to communicate with them
13 yourself?

14 A. Or Jim, myself or Jim.

15 (WHEREUPON, a certain document was
16 marked Nabulsi Deposition Exhibit
17 No. 29, for identification, as of
18 1-24-2007.)

19 MR. ZWICKER: Exhibit 29 before the witness is
20 a letter dated June 21, 2001, from Azmi Nabulsi to
21 Dr. Jan Schellens.

22 BY MR. ZWICKER:

23 Q. Do you recognize this as a letter you
24 wrote?

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 A. Yes.

2 Q. You say in the second

3 paragraph, "Unfortunately, it's been decided to

4 cease development of ABT-518 compound at this time.

5 This decision was made after careful consideration

6 of the clinical characterization of this class of

7 compound and its business implications."

8 This letter is dated June 21, 2001,

9 right?

10 A. Correct.

11 Q. Why is it that you waited more than two

12 weeks to inform Dr. Schellens of the termination?

13 MR. PHILLIPS: Object to the form; assumes

14 facts -- assumes facts not in the record.

15 BY THE WITNESS:

16 A. The only thing I could think of it's

17 like the first time. I wasn't pleased with the

18 decision to stop. So, most likely was working with

19 Perry to reverse the decision again before we stop.

20 BY MR. ZWICKER:

21 Q. Do you have a recollection of working

22 with Dr. Nisen to reverse Leiden's decision again?

23 A. You know, I don't really recall the

24 specifics. But I'm sure I sat with him and the

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 2001.

2 BY MR. ZWICKER:

3 Q. Do you see that?

4 A. Yes.

5 Q. You're not copied on the letter. Have

6 you ever seen it before?

7 A. No.

8 Q. You testified earlier today that you

9 learned that ABT-518 had been terminated in May or

10 early June of 2001, correct?

11 A. Correct.

12 Q. Do you know why it was that Abbott did

13 not inform Hancock until September 20 --

14 A. No.

15 Q. -- of the fact that ABT-518 had been

16 terminated?

17 MR. PHILLIPS: Objection to the form; assumes

18 facts not in the record.

19 BY THE WITNESS:

20 A. I had no interaction regarding the

21 Hancock. Hancock deal as a whole was invisible to

22 me.

23 (WHEREUPON, a certain document was

24 marked Nabulsi Deposition Exhibit

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 No. 34, for identification, as of

2 01-24-2007.)

3 MR. ZWICKER: Before the witness is Nabulsi --

4 MR. PHILLIPS: I'm sorry. I seem to have your

5 copy.

6 MR. ZWICKER: No, you don't.

7 MR. PHILLIPS: Oh, okay.

8 MR. ZWICKER: I just wrote on it.

9 MR. PHILLIPS: Okay.

10 MR. ZWICKER: Before the witness is Nabulsi

11 Exhibit No. 34, which is a memo dated August 10,

12 2001 from Steven K. Davidsen to Perry Nisen.

13 BY MR. ZWICKER:

14 Q. Dr. Nabulsi, do you recognize this

15 document?

16 A. I believe I have seen a version of this,

17 yes.

18 Q. What's the subject matter of this

19 document?

20 MR. PHILLIPS: Objection to the form. It

21 speaks for itself. The document speaks for itself.

22 BY MR. ZWICKER:

23 Q. Put it this way. What -- what do you

24 understand the discussion about 518 that is

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 stated anyway.

2 BY THE WITNESS:

3 A. Share what?

4 BY MR. ZWICKER:

5 Q. Did Dr. Nisen share the view that

6 development of 518 should continue notwithstanding

7 the results of ASCO?

8 MR. PHILLIPS: Object to the form; calls for

9 speculation.

10 BY MR. ZWICKER:

11 Q. Do you know?

12 A. Perry was in agreement with me. About

13 your question about share, I'm not sure share with

14 whom?

15 Q. Let me ask the question a different way.

16 Did Dr. Nisen tell you that he believed

17 that development of ABT-518 should continue

18 notwithstanding the results of ASCO?

19 A. Yes.

20 Q. Did Dr. Nisen ever tell you that he

21 believed the ASCO results did not provide

22 substantial bad data in connection with ABT-518?

23 MR. PHILLIPS: Objection to the form.

24 BY THE WITNESS:

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 A. I don't recall the exact words -- the
2 exact words, but Perry, myself, Steve were
3 generally in agreement to proceed.

4 BY MR. ZWICKER:

5 Q. And did Dr. Nisen tell you that he
6 thought the results at ASCO were not definitive for
7 the development of ABT-518?

8 MR. PHILLIPS: Object to the form.

9 BY THE WITNESS:

10 A. I don't recall the exact words, if he
11 said those exact words.

12 BY MR. ZWICKER:

13 Q. Did he say something to that effect?

14 A. Based on his position, yes.

15 MR. ZWICKER: I may have no further questions.

16 If we could take just a few minute break and --

17 MR. PHILLIPS: Sure.

18 THE VIDEOGRAPHER: Going off the record. The
19 time now is 5:03 p.m.

20 (WHEREUPON, a recess was had
21 from 5:03 to 5:10 p.m.)

22 THE VIDEOGRAPHER: We're back on the record at
23 5:10 p.m.

24 MR. ZWICKER: Dr. Nabulsi, I have no further

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 UNITED STATES DISTRICT COURT
2 FOR THE DISTRICT OF MASSACHUSETTS

3

4 JOHN HANCOCK LIFE INSURANCE)
5 COMPANY, JOHN HANCOCK VARIABLE)
6 LIFE INSURANCE COMPANY and)
7 MANULIFE INSURANCE COMPANY)
8 (f/k/a INVESTORS PARTNER)
9 INSURANCE COMPANY),)

10 Plaintiffs,) Civil Action No.

11 -vs-) 05-11150-DPW

12 ABBOTT LABORATORIES,)

13 Defendant.)

14

15 I hereby certify that I have read the
foregoing transcript of my deposition given at the
16 time and place aforesaid, consisting of Pages 1 to
295, inclusive, and I do again subscribe and make
17 oath that the same is a true, correct and complete
transcript of my deposition so given as aforesaid,
18 and includes changes, if any, so made by me.

19

20 AZMI NABULSI

21 SUBSCRIBED AND SWORN TO

22 before me this day

23 of , A.D. 200__.

24 Notary Public

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 STATE OF ILLINOIS)

2) SS:

3 COUNTY OF DU PAGE)

4 I, CORINNE T. MARUT, C.S.R. No. 84-1968,

5 a Notary Public within and for the County of

6 DuPage, State of Illinois, and a Certified

7 Shorthand Reporter of said state, do hereby

8 certify:

9 That previous to the commencement of the

10 examination of the witness, the witness was duly

11 sworn to testify the whole truth concerning the

12 matters herein;

13 That the foregoing deposition transcript

14 was reported stenographically by me, was thereafter

15 reduced to typewriting under my personal direction

16 and constitutes a true record of the testimony

17 given and the proceedings had;

18 That the said deposition was taken

19 before me at the time and place specified;

20 That the reading and signing by the

21 witness of the deposition transcript was agreed

22 upon as stated herein;

23 That I am not a relative or employee or

24 attorney or counsel, nor a relative or employee of

Nabulsi, Azmi (NEW USE THIS ONE) 1/24/2007 12:00:00 AM

1 such attorney or counsel for any of the parties

2 hereto, nor interested directly or indirectly in

3 the outcome of this action.

4 IN WITNESS WHEREOF, I do hereunto set my

5 hand and affix my seal of office at Chicago,

6 Illinois, this 30th day of January, 2007.

7

8

9

10 CORINNE T. MARUT, C.S.R. No. 84-1968

11 Notary Public, DuPage County, Illinois.

12 My commission expires August 15, 2009.

13

14

15

16

17

18

19

20

21

22

23

24

AZMINABULSI, JANUARY 24, 2007

197391

1 UNITED STATES DISTRICT COURT
 2 FOR THE DISTRICT OF MASSACHUSETTS
 3

4 JOHN HANCOCK LIFE INSURANCE)
 5 COMPANY, JOHN HANCOCK VARIABLE)
 6 LIFE INSURANCE COMPANY and)
 7 MANULIFE INSURANCE COMPANY)
 8 (f/k/a INVESTORS PARTNER)
 9 INSURANCE COMPANY),)

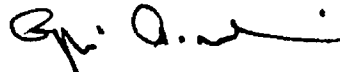
10 Plaintiffs,) Civil Action No.

11 -vs-)

05-11150-DPW

12 ABBOTT LABORATORIES,)
 13 Defendant.)

14
 15 I hereby certify that I have read the
 16 foregoing transcript of my deposition given at the
 17 time and place aforesaid, consisting of Pages 1 to
 18 295, inclusive, and I do again subscribe and make
 19 oath that the same is a true, correct and complete
 20 transcript of my deposition so given as aforesaid,
 21 and includes changes, if any, so made by me.

22 

AZMI NABULSI

21 SUBSCRIBED AND SWORN TO

22 before me this 23 day

23 of Feb. , A.D. 2007.

24 Notary Public

AZMI NABULSI, JANUARY 24, 2007

12:17:36 1 were directed to cease all development activities
12:17:40 2 for 518 by Dr. Leiden?

12:17:43 3 A. We were asked --

12:17:44 4 MR. PHILLIPS: Objection; asked and answered.

12:17:45 5 BY THE WITNESS:

12:17:45 6 A. We were asked to stop 518. ~~I don't -- I~~
12:17:50 7 ~~don't recall the exact nature and the language of~~
12:17:53 8 ~~the order.~~ It came to me through from Perry. I
12:17:56 9 never -- did not talk to Jeff Leiden directly.

12:18:00 10 MR. ZWICKER: Let's mark as the next exhibit
12:18:08 11 these two, and we're going to mark them in this
12:18:12 12 order.

12:18:12 13 (WHEREUPON, certain documents were
12:18:12 14 marked Nabulsi Deposition Exhibit
12:18:12 15 Nos. 12 and 13, for identification,
12:18:37 16 as of 01-24-2007.)

12:18:37 17 BY MR. ZWICKER:

12:18:38 18 Q. I'd like you, Dr. Nabulsi, to review
12:18:41 19 Nabulsi Exhibit No. 12, which is a typewritten
12:18:46 20 document to Jim from Azmi bearing Bates
12:18:56 21 No. ABBT0507886 and take a look at it.

12:19:09 22 MR. ZWICKER: Let's go off the record for one
12:19:11 23 minute.

12:19:12 24 THE VIDEOGRAPHER: Going off the record. The

AZMINABULSI, JANUARY 24, 2007

12:32:57 1 the instruction from Perry Nisen to stop all
12:33:01 2 development activities, did you believe that
12:33:03 3 instruction was permanent?

12:33:09 4 MR. PHILLIPS: Object to the form.

12:33:10 5 MR. ZWICKER: Let me ask it again.

12:33:12 6 BY MR. ZWICKER:

12:33:13 7 Q. Did you believe that the termination of
12:33:16 8 development activities for ABT-518 was temporary or
12:33:22 9 permanent?

12:33:24 10 MR. PHILLIPS: Objection to the form.

12:33:25 11 BY THE WITNESS: *Permanent.*

12:33:26 12 A. *My discussion with Perry at the time*
12:33:29 13 *that we need to rechallenge the decision or the*
12:33:33 14 *instructions. So, whether it was permanent or not.*
12:33:39 15 ~~Obviously I don't know if it's the same between~~
12:33:49 16 ~~permanent and terminate,~~ but our decision was to
12:33:54 17 rechallenge.

12:33:55 18 BY MR. ZWICKER:

12:33:55 19 Q. Okay. But in your mind the instruction
12:33:56 20 from Dr. Leiden was not a temporary decision? It
12:34:00 21 was a permanent decision?

12:34:00 22 A. That's right.

12:34:01 23 MR. PHILLIPS: Objection. I'm sorry.

12:34:01 24 THE WITNESS: I'm sorry.

AZMINABULSI, JANUARY 24, 2007

12:34:01 1 MR. PHILLIPS: Dr. Nabulsi, please give me
12:34:01 2 just a moment.
12:34:01 3 THE WITNESS: Okay. Go ahead.
12:34:03 4 MR. PHILLIPS: Object to the form.
12:34:03 5 BY MR. ZWICKER:
12:34:03 6 Q. Go ahead and answer.
12:34:09 7 A. You don't stop a study and start again.
12:34:14 8 It's an -- it's an important event. We did not
12:34:17 9 know if Jeff understands that and what his clear
12:34:22 10 instructions. So we need to challenge. Our -- our
12:34:25 11 intention was to rechallenge his decision.
12:34:27 12 Q. But you took his directive as a final
12:34:29 13 decision to terminate the 518 program?
12:34:32 14 MR. PHILLIPS: Object to the form;
12:34:33 15 mischaracterizes the testimony.
12:34:34 16 BY THE WITNESS: *yes as final.*
12:34:36 17 A. ~~I don't recall how I took the decision~~
12:34:37 18 I wasn't happy with the decision and we decide to
12:34:40 19 rechallenge it.
12:34:41 20 BY MR. ZWICKER:
12:34:41 21 Q. But in your own mind when you received
12:34:43 22 his instruction, you viewed his instruction as a
12:34:51 23 final decision. True?
12:34:52 24 MR. PHILLIPS: Object to the form; asked and

AZMINABULSI, JANUARY 24, 2007

13:41:56 1 development based on competitor data?

13:41:59 2 MR. PHILLIPS: Object to the -- objection to
13:42:01 3 the form.

13:42:02 4 BY THE WITNESS:

13:42:02 5 A. No.

13:42:02 6 BY MR. ZWICKER:

13:42:03 7 Q. What did you tell her?

13:42:04 8 A. That Jeff Leiden instructed Perry who
13:42:06 9 told me to stop ~~enrolling patients~~ ^{development of 318}

13:42:13 10 Q. What was her response?

13:42:16 11 A. Not happy. She followed the
13:42:21 12 instructions, but logistically that's a complicated
13:42:25 13 thing.

13:42:25 14 Q. How? Why was it logistically
13:42:28 15 complicated?

13:42:29 16 A. Because we just started.

13:42:31 17 Q. At some point in -- on or around the
13:42:36 18 12th, you had a conversation with Professor
13:42:39 19 Schellens about the halt on the clinical trial. Do
13:42:41 20 you recall that?

13:42:44 21 MR. PHILLIPS: Object to the form.

13:42:46 22 BY THE WITNESS:

13:42:47 23 A. I don't recall one-one discussion with
13:42:53 24 Schellens about that time.

AZMINABULSI, JANUARY 24, 2007

13:44:21 1 of today, and Ms. D'Amico provides your name and
13:44:27 2 says that you will call in the morning. Is that
13:44:30 3 about a proper summary?

13:44:33 4 A. Dr. Schellens. You said Dr. Nabulsi.

13:44:36 5 Q. Ah, Schellens. Correct.

13:44:39 6 A. That's right.

13:44:40 7 Q. Do you recall having a conversation with
13:44:43 8 Professor Schellens, the first conversation you had
13:44:46 9 with him after the clinical trial had been halted?

13:44:51 10 A. I don't recall, you know, the actual
13:44:54 11 conversation. But I'm certain that I did talk to
13:44:59 12 him because that's my job, to communicate with him.
~~Actually, I did not recall having a conversation with him.~~

13:45:01 13 Q. What did you tell him about the reasons
13:45:04 14 for the shutdown of the clinical trial?

13:45:05 15 A. Would have been the same reasons, the
13:45:07 16 priority of the portfolio and the competition.

13:45:12 17 Q. What was his response?

13:45:14 18 A. He was very displeased.

13:45:17 19 Q. What did he say?

13:45:19 20 A. That this is not the appropriate thing
13:45:20 21 to do.

13:45:22 22 Q. What did he suggest doing instead?

13:45:26 23 A. That he still wanted to communicate with
13:45:30 24 Abbott highest ranking officer or highest ranking

AZMINABULSI, JANUARY 24, 2007

14:11:10 1 BY MR. ZWICKER:

14:11:10 2 Q. Well, let me -- let me ask it this way.
14:11:12 3 Did you know in March of 2001 that Dr. Leiden had
14:11:17 4 put all development activities with the exception
14:11:19 5 of the clinical trial on hold?

14:11:21 6 MR. PHILLIPS: Object to the form.

14:11:22 7 BY THE WITNESS:

14:11:23 8 A. ~~I don't recall.~~ Yes

14:11:23 9 BY MR. ZWICKER:

14:11:23 10 Q. ~~You don't recall?~~

14:11:24 11 A. ~~I don't recall.~~

Based on
above charge.

14:11:26 12 Q. You would agree with me that as the
14:11:29 13 venture head for 518, that would have been a fact
14:11:32 14 that you would have been very interested in
14:11:34 15 learning, correct?

14:11:35 16 A. Absolutely.

14:12:28 17 (WHEREUPON, a certain document was
14:12:28 18 marked Nabulsi Deposition Exhibit
14:12:28 19 No. 17, for identification, as of
14:12:30 20 01-24-2007.)

14:12:30 21 MR. ZWICKER: The record should reflect that
14:12:32 22 before the witness is Nabulsi Exhibit No. 17, which
14:12:34 23 is a chain of e-mails dated May 25, 2001.

14:12:34 24 BY MR. ZWICKER:

AZMINABULSI, JANUARY 24, 2007

14:18:28 1 continued to be on hold after the clinical trial
14:18:35 2 halt was lifted?

14:18:36 3 MR. PHILLIPS: Object to the form.

14:18:45 4 BY THE WITNESS:

14:18:45 5 A. I don't want to speculate or guess.

14:18:47 6 BY MR. ZWICKER:

14:18:47 7 Q. I don't want you to.

14:18:49 8 A. Yeah. It's -- any toxicology activity,
14:18:52 9 that would have been -- that would have been -- to
14:18:57 10 be conducted would not have been essential to the
14:18:59 11 program. So, whether I asked for it to stop or not
14:19:02 12 was not really key at the time or whether Jeff
14:19:05 13 asked for it to stop or not wasn't key for the
14:19:08 14 program.

14:19:08 15 Q. Okay. I understand that that's your
14:19:10 16 opinion. My question to you was only: Isn't it
14:19:15 17 true that certain aspects of the development
14:19:17 18 process for 518 remained on hold after March 2001?

14:19:22 19 MR. PHILLIPS: Object to the form.

14:19:30 20 BY THE WITNESS:

14:19:31 21 A. ~~Yes. I don't recall if I'm going to answer~~
14:19:35 22 ~~correctly, I can't recall exactly what were the~~
14:19:36 23 ~~instructions to all parties of the team.~~

14:19:39 24 BY MR. ZWICKER:

AZMINABULSI, JANUARY 24, 2007

14:20:34 1 A. ^{Yes} ~~This raises suspicion or it raises a~~
14:20:37 2 ~~question that the program may have been on hold.~~
14:20:41 3 ~~But till Diane answers, I don't know for sure. I~~
14:20:45 4 ~~cannot recall for sure.~~

14:20:45 5 BY MR. ZWICKER:

14:20:45 6 Q. All right. I just want the record to be
14:20:48 7 clear about your knowledge.

14:20:49 8 Do you recall one way or another whether
14:20:55 9 other development activities for 518 remained on
14:20:59 10 hold after March 13, 2001?

14:21:03 11 MR. PHILLIPS: Object to the form. You mean
14:21:04 12 other than the clinical trial?

14:21:06 13 .. MR. ZWICKER: Other than the clinical trial.
14:21:07 14 BY THE WITNESS:

14:21:08 15 A. Can you repeat that, please?

14:21:09 16 BY MR. ZWICKER:

14:21:09 17 Q. Yeah. With Mr. Phillips' amendment, do
14:21:17 18 you remember whether other aspects of the
14:21:21 19 development of 518 remained on hold after March 13,
14:21:27 20 2001?

14:21:28 21 A. Yes.

14:21:29 22 Q. What remained on hold?

14:21:31 23 A. I believe we did not start the IND
14:21:36 24 study.

AZMINABULSI, JANUARY 24, 2007

16:32:20 1 A. Correct.

16:32:21 2 Q. So, it's fair to say that the results of
16:32:23 3 the Phase I clinical trial had no impact on the
16:32:28 4 decision to terminate ABT-518?

16:32:32 5 MR. PHILLIPS: Objection to the form.

16:32:33 6 BY THE WITNESS:

16:32:33 7 A. We did not have any results at the time.

16:32:35 8 BY MR. ZWICKER:

16:32:35 9 Q. So, the trial could not have played any
16:32:39 10 role in the decision. Fair?

16:32:40 11 MR. PHILLIPS: Objection to the form. You're
16:32:41 12 talking about the results of the trial?

16:32:42 13 MR. ZWICKER: Correct.

16:32:43 14 BY THE WITNESS:

16:32:44 15 A. Yeah, correct, non-existent.

16:33:17 16 BY MR. ZWICKER:

16:33:17 17 Q. Did you inform the clinical sites of
16:33:20 18 Dr. Leiden's decision?

16:33:24 19 MR. PHILLIPS: Dr. Nabulsi personally?

16:33:28 20 MR. ZWICKER: Yes.

16:33:28 21 BY THE WITNESS:

16:33:30 22 A. Well, I informed them through Jim first,
16:33:33 23 initially. *then flew to Netherlands + met with Schellens + Zonnenberg face to face (separately)*

16:33:34 24 BY MR. ZWICKER:

AZMI NABULSI, JANUARY 24, 2007

16:36:51 1 Q. Jim Looman?

16:36:52 2 A. That's right.

16:36:56 3 Q. Your response to Ms. D'Amico is to

16:36:59 4 direct her not to communicate with the sites yet.

16:37:03 5 Do you see that?

16:37:04 6 A. That's right.

16:37:05 7 Q. Why did you want her to delay?

16:37:09 8 MR. PHILLIPS: Objection to the form.

16:37:16 9 BY THE WITNESS:

16:37:16 10 A. I don't recall.

16:37:17 11 BY MR. ZWICKER:

16:37:18 12 Q. Did you want to communicate with them

16:37:19 13 yourself?

16:37:21 14 A. ~~Or Jim, myself or Jim~~ *Yes. I had Jim communicate first, then I met with them.*

16:37:21 15 (WHEREUPON, a certain document was *performed in NL*

16 16 marked Nabulsi Deposition Exhibit

17 17 No. 29, for identification, as of

16:37:58 18 1-24-2007.)

16:37:58 19 MR. ZWICKER: Exhibit 29 before the witness is

16:38:00 20 a letter dated June 21, 2001, from Azmi Nabulsi to

16:38:05 21 Dr. Jan Schellens.

16:38:05 22 BY MR. ZWICKER:

16:38:08 23 Q. Do you recognize this as a letter you

16:38:10 24 wrote?

AZMINABULSI, JANUARY 24, 2007

16:38:10 1 A. Yes.

16:38:14 2 Q. You say in the second

16:38:16 3 paragraph, "Unfortunately, it's been decided to
16:38:17 4 cease development of ABT-518 compound at this time.
16:38:21 5 This decision was made after careful consideration
16:38:23 6 of the clinical characterization of this class of
16:38:26 7 compound and its business implications."

16:38:30 8 This letter is dated June 21, 2001,
16:38:33 9 right?

16:38:33 10 A. Correct.

16:38:34 11 Q. Why is it that you waited more than two
16:38:37 12 weeks to inform Dr. Schellens of the termination?

16:38:40 13 MR. PHILLIPS: Object to the form; assumes
16:38:43 14 facts -- assumes facts not in the record.

16:38:45 15 BY THE WITNESS:

16:38:49 16 A. The only thing I could think of it's
16:38:52 17 like the first time. I wasn't pleased with the
16:38:55 18 decision to stop. So, most likely was working with
16:39:01 19 Perry to reverse the decision again before we stop.

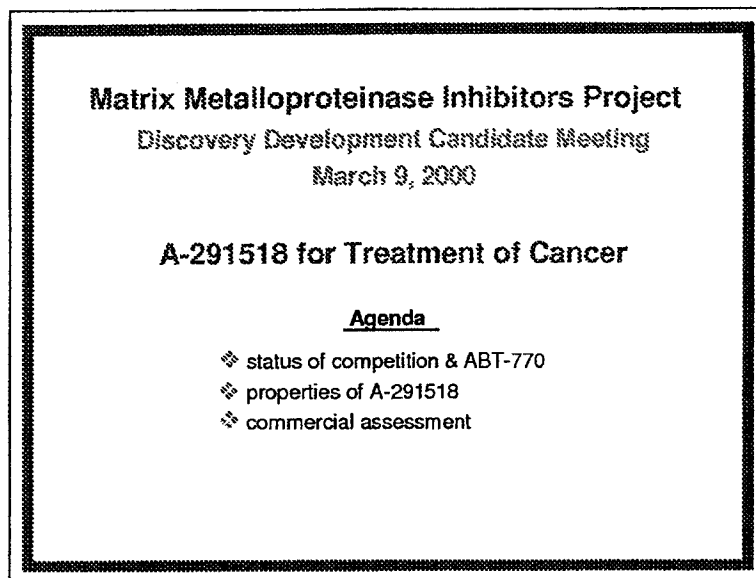
16:39:04 20 BY MR. ZWICKER: *We would explain that it is inappropriate as well, take
into account the March events.*

16:39:04 21 Q. Do you have a recollection of working
16:39:06 22 with Dr. Nisen to reverse Leiden's decision again?

16:39:10 23 A. You know, I don't really recall the
16:39:11 24 specifics. But I'm sure I sat with him and the

Deposition Exhibit No. 1

P's Exhibit B



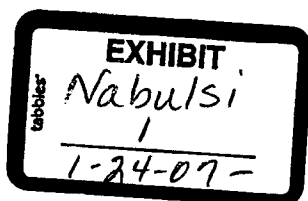
Good... I'll be covering Abbott's Follow-up MMP inhibitor to ABT-770 namely A-291518 which is intended for the treatment of cancer patients

I'll start with an update on Status of competition & ABT-770

Spend the bulk of our time describing the attributes of A-291518

then Lisa Lux will give her take on the commercial assessment of this compound

1



HIGHLY CONFIDENTIAL
ABBT0141929

Clinical MMP Inhibitors Selectivity versus Joint Toxicity						
MMP Inhibitor Company	Development Stage; Indication	Enzyme Inhibition IC ₅₀ (nM)				Clinical Joint Toxicity
		gel. A MMP-2	gel. B MMP-9	fib. coll. MMP-1	TACE	
marimastat British Biotech/ Schering-Plough	Phase III cancer	0.41	0.79 <i>broad spectrum</i>	0.78	1.8	yes
prinomastat Agouron/ Warner-Lambert	Phase III cancer	0.05	0.05 <i>modestly selective</i>	5.7	7.9	yes
BMS 275291 Bristol-Myers Squibb/ Chirosciences	Phase II cancer	41	25 <i>broad spectrum</i>	9	inactive	yes
BAY 12-9566 Bayer	Phase III cancer/arthritis WITHDRAWN	120	1,600 <i>highly selective</i>	>30,000	>30,000	no

As you know, one of the key issues in the MMP inhibitors field relates to the dose-limiting joint toxicity exhibited by all three of the most advanced compounds.

The cause of the side effect is still NOT known yet I'd say the most widely held opinion is that it is due to a disruption in collagen turnover caused by reduction in collagenolytic activity

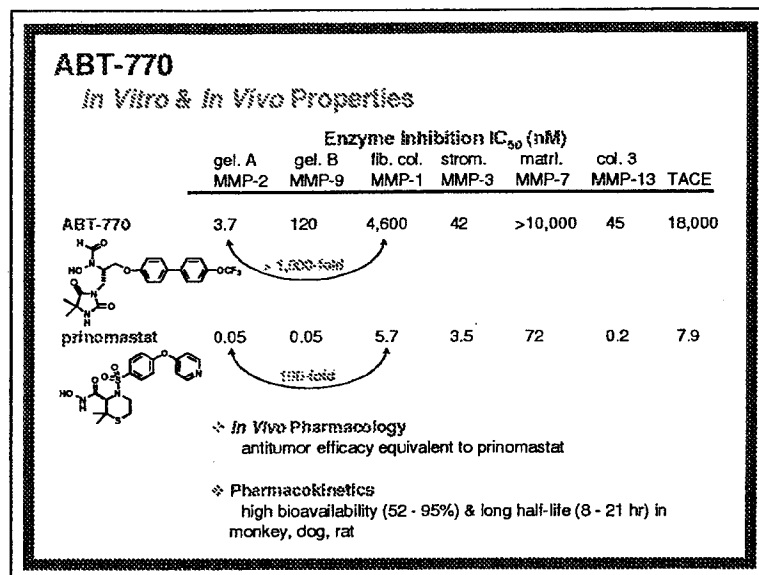
This may be a consequence of fib. coll. inhibition given its ability to degrade helical collagen and the IC₅₀s shown here are consistent with this idea.

You are aware of the joint effects produced by mar. prin. and the lack thereof from the highly selective agent from Bayer.

The data we haven't talked about comes from a collaboration between Chirosciences and BMS on BMS 275291. They speculated that inhibition of "shedases" like TNF-conv. or TACE may be responsible...so they identified a compound with broad MMP inhibition which lacks TACE activity. Unfortunately for them, joint effects were indeed observed in multiple-dose Phase I studies with this compound.

This is consistent with our hypothesis that gelatinase selective agents which does not alter collagenolytic activity, will be efficacious without producing joint effects.

I'd like to first provide an update on each of these compounds, starting with marimastat.....



I briefly want to discuss the status of ABT-770, just so everyone understands what happened with this compound...

The reasons we became interested in ABT-770 is shown here.

See that it is 10-fold MORE selective for the inhibition of gel A versus fib. coll. than prinomastat...

Despite this enhanced selectivity it produces equivalent antitumor effects in pre-clinical models.

In addition, ABT-770 produces high and sustained plasma concentrations following oral doses in a variety of species.

ABT-770 Safety						
4-Week GLP Toxicity Studies						
	Rat			Monkey		
	Dose (mg/kg/day)			Dose (mg/kg/day)		
	10	30	100	20	60	180
Secondary Findings						
leukopenia/reticulocytopenia			X			
bone marrow hypocellularity	n/e	n/e	X			
altered serum chemistry			X		X	X
Primary Findings						
phospholipidosis - lungs, lymph nodes, liver	X	X	X	X	X	X
apoptosis of glandular epithelium - stomach		X	X	X	X	X
Clinical Observations						
↓ activity			X		X	X
dehydration/emaciation, ↓ body weight			X		X	X
lethality			X		X	X
n/e = not evaluated						
❖ ABT-770 did NOT clear 100 mg/kg/day in rats and 60 mg/kg/day in monkeys						

The reason we became Disinterested in ABT-770 is shown here

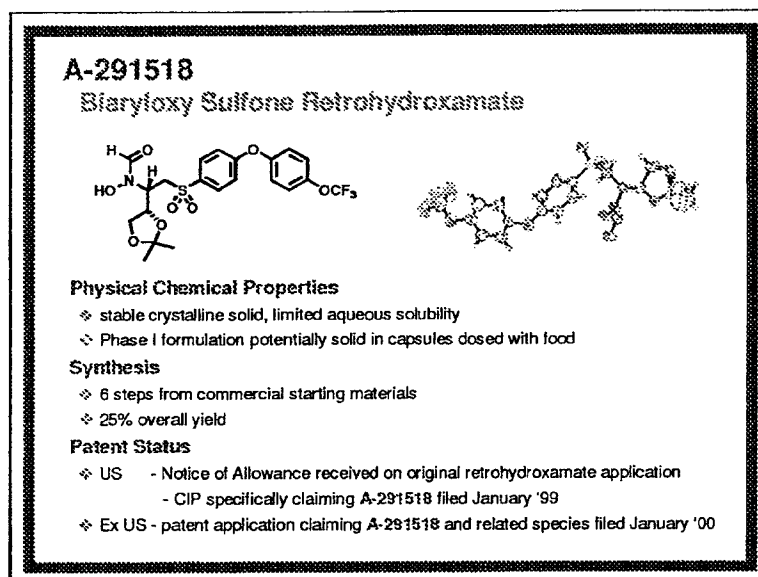
That is, it produced a number of adverse effects given orally at high dose to rats and monkeys over 4-weeks

- reduction in white blood cell count seen in rats
- phospholipidosis seen in a variety of tissues in both rats and monkeys

plus - loss in body weight and lethality

Occured at 100 mg/kg/day in rats and 60 mg/kg/day in monkeys which, as you'll see, reduced our therapeutic window significantly SO.... the development of the compound was terminated last November.

That brings us to the reason we are here today, namely A-291518.....

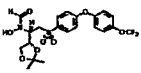
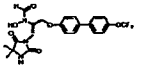
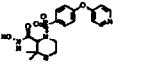


A-291518 is a member of the Biaryloxy Sulfone class of retrohydroxamate MMP inhibitors..... its structure is shown here.

The compound is a stable crystalline solid, which, like ABT-770, has limited aqueous solubility which translates into a slow dissolution.

As we'll see later, food assists with the absorption of 518, suggesting a potential Phase I formulation of solid in capsules dosed with food.

A-291518 can be synthesized in 6 steps from commercial starting materials in 25% overall yield..... Given these starting materials, Steve Wittenberger and Steve King have promised to deliver 4 kg by sometime in June.

Enzyme Inhibition Potent & Selective		Enzyme inhibition IC ₅₀ (nM)						
		gel. A MMP-2	gel. B MMP-9	fib.col. MMP-1	strom. MMP-3	matrl. MMP-7	col. 3 MMP-13	TACE
A-291518		0.78	0.50	8,900	12	11,000	3.3	340
ABT-770		3.7	120	4,600	42	>10,000	45	18,000
prinomastat		0.05	0.05	5.7	3.5	72	0.20	7.9

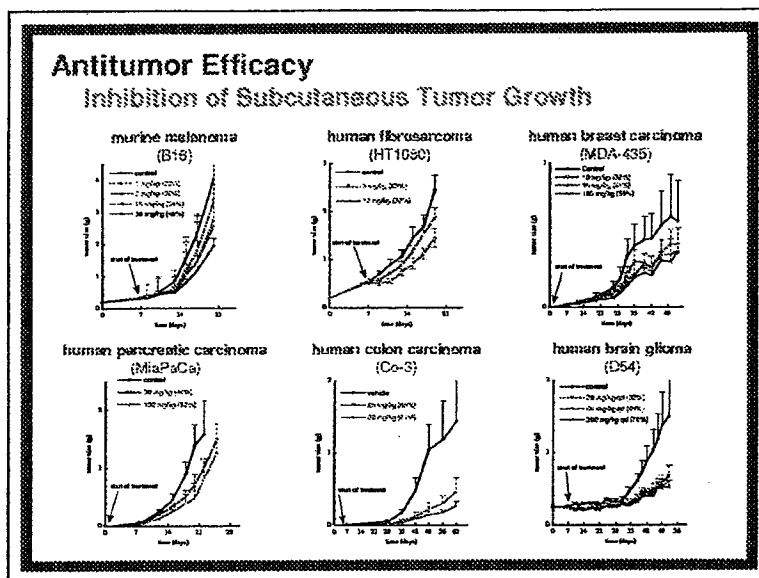
* 200-fold more potent versus gelatinase B than ABT-770
 * 100-fold more selective (gelatinase A vs. fib. collagenase) than prinomastat

IC₅₀ values for inhibition of various MMPs and TACE are shown here for A-291518, ABT-770 and prinomastat.

A-291518 is a subnanomolar inhibitor of both gelatinases, some potency with respect to strom and MMP-13.... limited potency versus TACE, matrylsin and fib. coll.

See here that A-291518 is 200-fold more potent than ABT-770 with respect to gelatinase B and 100-times more selective for the inhibition of gel A than fib. coll. relative to prinomastat.

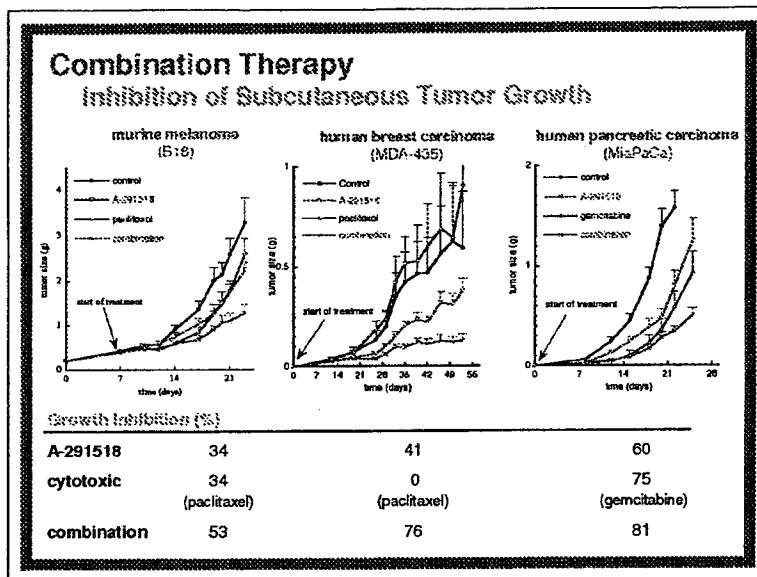
Despite this enhanced selectivity, A-291518 produces dose-dependent effects in animal models of tumor growth.



Six of those models are shown here - the idea is not analyze each on but rather to illustrate the diversity of conditions under which A-291518 slows the growth of tumors... these models include...

- syngeneic models, human tumor xenografts
- growth of tumor in the flank, growth of tumor at orthotopic sites
- slow growing tumors, faster growing tumors....
- dosing initiated at Day zero, dosing initiated at Day 7

These models all use A-291518 as a single agent, yet it is also efficacious when dosed in combination with cytotoxic agents...



Shown here is the effect of A-291518 on tumor growth in three models given as

- single agent (green)
- cytotoxic agent given as a single agent (blue)
- A-291518 plus cytotoxic agent (red)

in each case, combination therapy producing greater growth suppression than either agent dosed alone.

Antitumor Efficacy in Mice			
Summary			
Model	Percent Inhibition of Control¹ (30 mg/kg, po, bid)		
	prinomastat	ABT-770	A-291518
subcutaneous growth - B16	51±7	51±9	44±6
mouse melanoma			
subcutaneous growth - HT1080	25	25±1	37±13
human fibrosarcoma			
subcutaneous growth - MiaPaCa	40	29	54±25
human pancreatic carcinoma			
subcutaneous growth - D54	58	nt ²	62 ³
human glioma			
orthotopic growth - MDA-435	nt ²	60	38
human breast carcinoma			
orthotopic growth - Co3	nt ²	82 ³	88 ³
human colon carcinoma			
cornea angiogenesis - bFGF induced	38±19	53±19	29±14
cornea angiogenesis - VEGF induced	75	23±4	43±9

1. Percent inhibition of control at 0.5 gram (MDA-435), 1 gram (MiaPaCa, Co3, D54), or 2 gram (B16, HT1080)

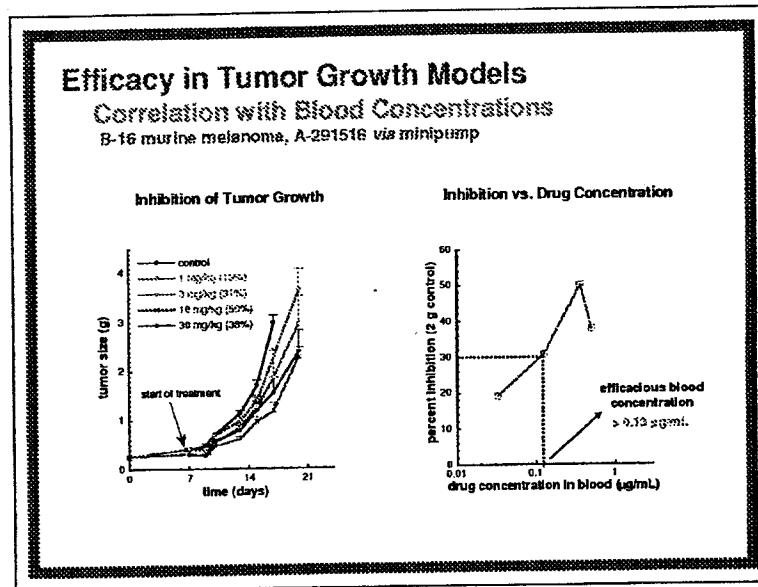
2. nt: not tested

3. compound administered at a dose of 20 mg/kg, qd

A comparison of the antitumor efficacy exhibited by A-291518 relative to ABT-770 and prinomastat is given in this summary.

These % inhibitions were generated by 30 mg/kg oral doses given twice daily except for D54 and Co3 studies which were qd.

As you can see, A-291518 may be more or less efficacious than ABT-770 and prinomastat in a given model, yet generally these compounds behave in a similar fashion including models of growth factor-induced angiogenesis in mouse cornea.



some MMPs more important than others.... therefore which to inhibit and which to spare?

A-291518

Plasma Protein Binding

❖ Centrifugation Studies plasma protein binding of A-291518

mouse plasma	94.4%	→ 7-fold greater "free" A-291518 in mouse versus human
human plasma	99.2%	

❖ Gelatinase Potency in the Presence of 80% Plasma

	A-291518 IC ₅₀ (truncated gelatinase A, nM)	fold-shift buffer vs. plasma
buffer	1.9	
human plasma	100	53
mouse plasma	??	??
rat plasma	??	??
monkey plasma	??	??

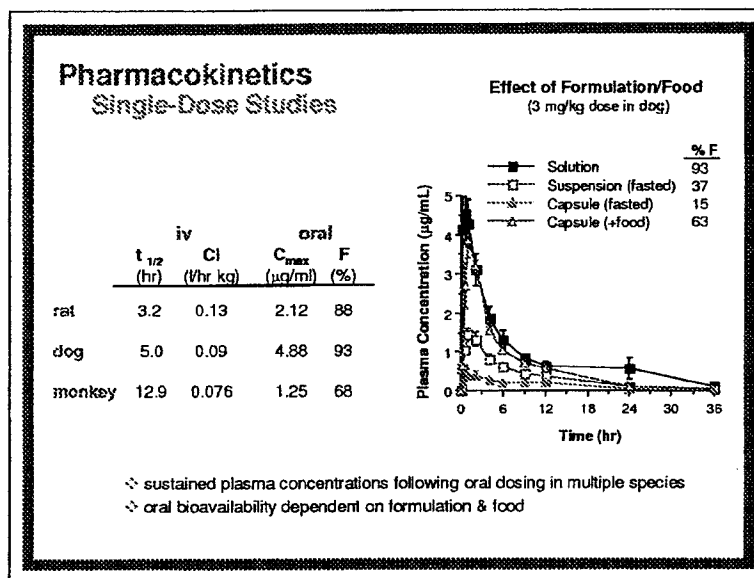
❖ Ramifications

- higher plasma concentrations required for human efficacy vs. mouse?
- "masking" of therapeutic window if protein binding in tox species is high relative to efficacy models?

We've measured the plasma binding of A-291518 via centrifugation in mouse and human plasma and the results are shown here. A-291518 is more highly protein bound in mouse than human plasma..... these numbers suggesting that there is 7-fold greater "free" A-291518 in mouse vs. human.

A more functional way to measure the effect of protein binding is to measure the shift in potency in the presence of human/mouse plasma. We've done that using a truncated version of gelatinase A and results shown here.....

The ramifications of these differences in shifts are.....



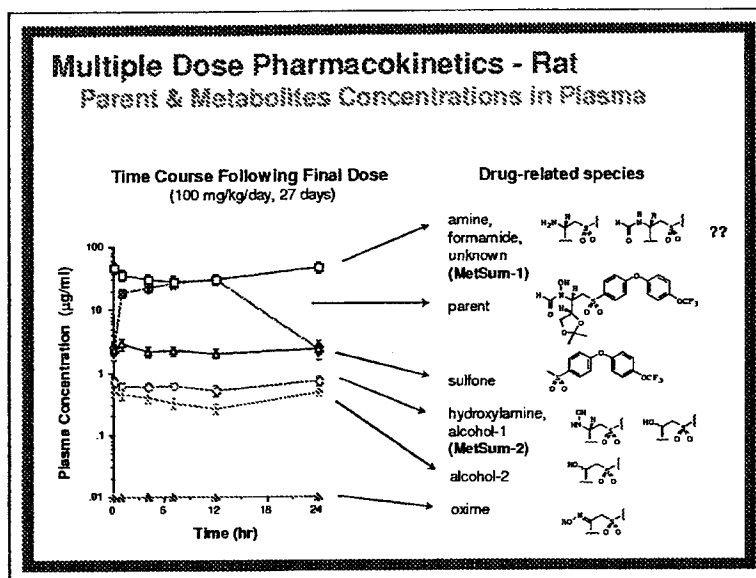
Moving on to PK,

The parameters for single-dose PK studies with A-291518 are given here...

- half-lives in rat, dog and monkey range from 3 to 13 hours
- the compound has low clearance values
- C_{max} s in the 1 to 5 μ g/ml range produced following 3 mg/kg oral doses
- bioavailabilities range between 68 to 93%

As you can see here, formulation and food has a effect on these bioavailability of A-291518 in dogs..... suspension and neat drug in a capsule being less well absorbed than the solution.

Dosing the capsule in the presence of food clearly assists in this absorption and suggests this as a possible Phase I formulation.



One of the key issues related to ALL the retrohydroxamates we've investigated so far is the production of metabolites following multiple oral dosing and I'll spend the next several slides going through the behavior of A-291518 in rats and monkeys analyzing concentration in both plasma and selected tissues.

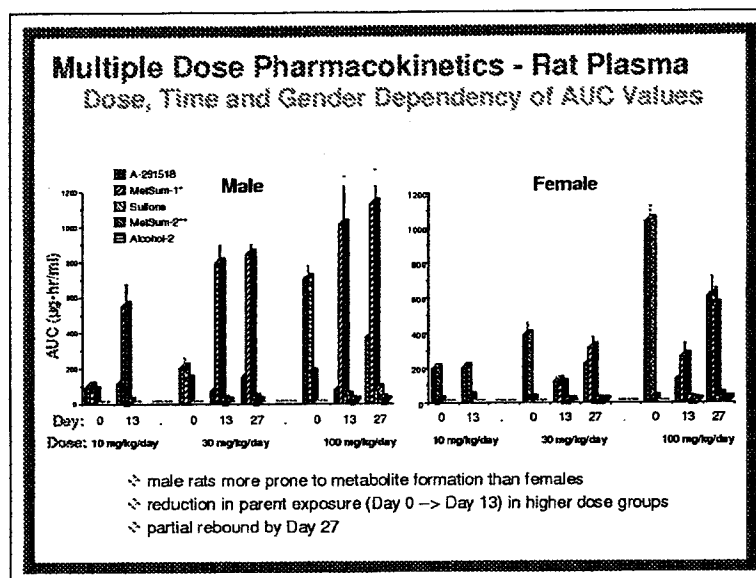
On the left you'll see a time course for A-291518 and its metabolites following the final dose in rats treated at 100 mg/kg/day over 4-weeks. At least 7 metabolites are formed, some of which are poorly resolved, thus the need to lump them together into MetSum-1 & -2.

The metabolites that we observed are generally the same ones we observed with ABT-770 suggesting a similar metabolic pathway. Most abundant is the mixture of the amine, formamide and an unknown which constitutes a greater percent of the total analytes than parent at 24 hours.

Also see the sulfone, hydroxylamine, alcohols - very little of the oximes are produced in rats.

The concentration of A-291518 and its metabolites in rat plasma is influenced by a number of factors including

- dose, the amount of time it was given and the gender of the rats.



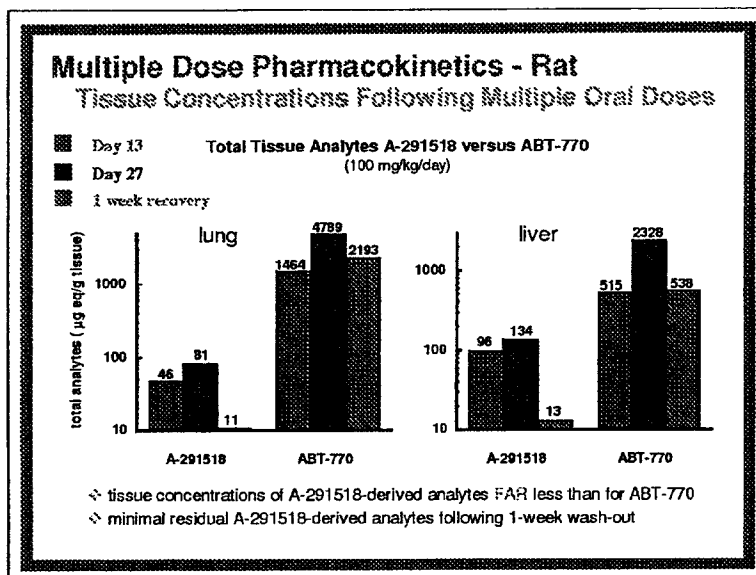
What I show here are AUC values parent (red) and metabolites (colors) given different doses of A-291518 in male (left) and female (right) rats. These doses are further broken into the Day of the study (Day 0, Day 13, Day 27).

First clear observation is that male rats are more prone to metabolite formation than females - black bars being much higher given the same Y-axis. Gender differences in metabolism in rodents are certainly well known and most likely revolve around differences in expression of cytochrome P450 isozymes.

For example, expression of CYP3A2 is 10-fold higher in males rats vs. females whereas CYP2C12 is 20-fold higher in females. While differences in CYP isoenzyme expression exists in humans, but they are

-not as great as in rodents and they differ between the two species.

The second observation we can make relates to the level of parent drug at different stages of the study. See in low dose male that parent AUC is the same on Day 0 as Day 13, both in males and females. AUCs for the 30 and 100 mg/kg doses, however fall over the same time interval. Interestingly, a partial rebound is seen in going from Day 13 to Day 27. Overall this is suggestive of induction of metabolizing enzymes at higher doses. We've run some preliminary Western blotting experiments and have seen induction of some CYP450 isozymes in whole cell extract from rats treated with A-291518. Clearly given the potential for drug/drug interaction, this will require further investigation - important to note that it happens at higher tox doses, not the 10 mg/kg dose.



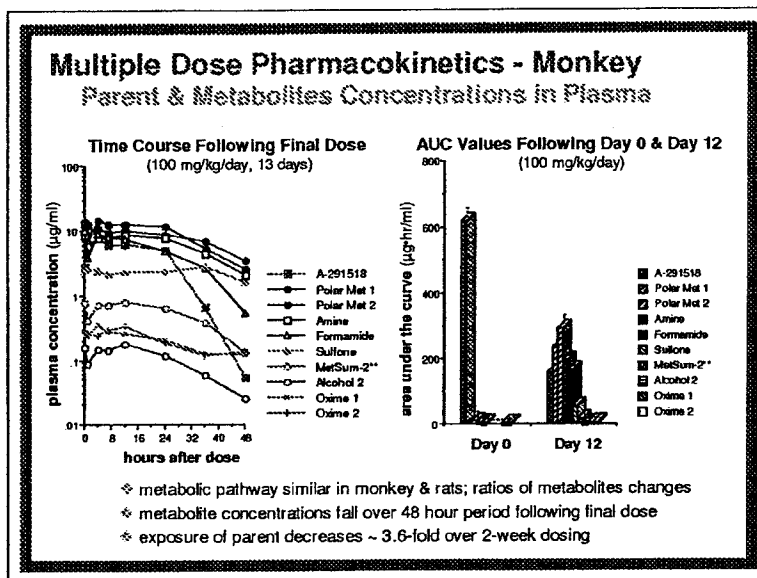
One of the other negative features of ABT-770 was then tendency of its metabolites to accumulate in certain tissues. In particular, millimolar concentrations of its amine metabolite were produced in lung tissue following dosing over 28 days.

Shown here is a comparison of the total analyte concentration, that is parent plus all metabolites, in lung and liver tissues for A-291518 and ABT-770 on Day 13, Day 27 and one week after the final dose of 100 mg/kg/day given to rats.

Important thing here is that we are using a log scale since the linear version would have sent the 770 values through the ceiling... clearly the total metabolite burden in these tissues is FAR less with A-291518 than with ABT-770.

Additionally, a large fall in metabolites occurs over the 1-week wash out period with only minimal quantities of metabolites of A-291518 remaining. Again, far different that with ABT-770.

So this is a clear differentiating feature of A-291518 over ABT-770 which most likely translates into a superior safety profile as well see later.

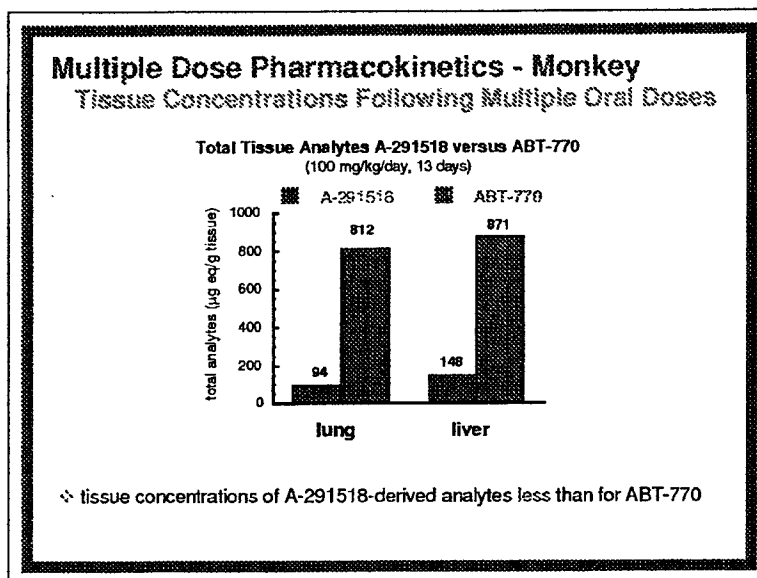


Moving now to monkeys dosed over 2-weeks with A-291518...

In monkey plasma we see many of the same metabolites as those produced in rats, with the exception of two polar metabolites which have not been identified thus far. Amine, formamide, sulfone....

Significantly, see a steady fall in metabolite concentrations during a 48-hour period following the final dose.

Similar to the rat, a 3.5-fold reduction in parent exposure is observed between Day 0 and Day 12. Remember, this is for a 100 mg/kg/day dose.... it will be interesting to see whether a similar fall occurs at a more "pharmacological" dose.



Tissue concentrations of parent and metabolites from those monkeys are shown here (lung & liver).....

While this is not a log scale, clearly see a substantial difference between the total analyte concentrations produced by A-291518 relative to ABT-770 and,

Again, this may be one of the reasons for benign toxicity profile of A-291518 relative to ABT-770.

A-291518 Safety
No Meaningful Issues
Genotoxicity
❖ non-mutagenic, non-clastogenic
Cytotoxicity
❖ cytotoxicity observed at high (> 40 μ M) concentrations only
Ligand Binding
❖ no substantial effects in 76 radioligand binding assays
CNS Safety
❖ no meaningful CNS effects in standard behavioral assays
CV Safety
❖ safe in anesthetized dog model through highest plasma concentration achieved (> 20 μ M)

Before we go on to the toxicity studies, a couple of, fortunately brief, words about about safety.....

A-291518 non-mutagenic and non-clastogenic

Cytotoxicity is observed only at high concentrations

It has no meaningful effect in a battery of 76 binding assays and no meaningful effects in standard CNS behavior assays.

And the compound is safe in an anesthetized dog model of CV safety through the highest plasma concentration achieved which was in excess of 20uM.

Toxicity Studies							
28-Day Oral Studies in Rat							
Compound AUC ₀₋₂₄ (µg-hr/ml)	Dose mg/kg /day	Mortality total deaths	Weight Gain (g) rat	Liver Wt. % total body wt.	WBC (E3/ µl)	Retic (E3/ µl)	Histopathology (# affected/# examined)
ABT-770							
2-week	0	0	11050	3.3	8.6	224	None
35/23	10	0	11249	3.3	8.1	235	None
170/118	50	0	9844	3.4	9.6	230	Lung: phospholipidosis (9/20)
403452	200	8	16214	4.0	3.7	97	Lung: phospholipidosis (21/21) Marrow: hypocellular (18/21)
4-week	0	0	16869	3.1	8.6	175	None
4041	10	0	16469	3.1	8.0	130	Not Examined
113/116	30	0	15767	3.1	9.8	185	Not Examined
439409	100	3	9113	3.9	3.6	122	Lung: phospholipidosis (15/16) Stomach: necrosis (4/22)
A-291518							
2-Week	0	0	3825	2.6	8.0	214	None
111/200	10	0	4424	3.2	10.0	235	Growth plate (2/10)
63/122	30	0	4030	3.6	10.3	227	Growth plate (5/10)
73/138	100	0	3524	4.2	10.8	305	Growth plate (9/10)
4-Week	0	-	13538	3.2	8.6	170	None
-	10	-	-	-	-	-	-
148/222	30	0	14362	3.2	5.9	196	Growth plate (1/10)
369/608	100	0	13356	4.4	9.7	304	Growth plate (4/10)

We've analyzed A-291518 in 2- and 4-weeks oral toxicity studies and those data are compared to ABT-770 here... ABT-770 2&4, 518 2&4; 4-week same doses, 2-week differ. As you can see, ABT-770 produced a number of effects at the high dose in both studies

- phospholipidosis, reticulocytopenia, leukopenia, reduction in weight gain and deaths.... the yellow indicates a doses which were NOT cleared.

A-291518 produces.....no evidence of phospholipidosis, no reduction in blood cell counts, no reduction in weight gain and no deaths. Significantly, the 4-week plasma concentrations being quite similar to those produced by ABT-770.

The high dose of A-291518 does cause an increase in liver weight which may be a consequence of induction of liver enzymes involved in its metabolism.

It also causes a thickening of the growth plate at all doses, the incidence appearing to be dose related. This lesion mimics the growth plate thickening observed in gelatinase B knockout mice which is thought to be a consequence of inhibition of the angiogenesis necessary for ossification. This lesion in gel-B KO mice resolves about 3-4 weeks after birth... interestingly the incidence of growth plate thickening with A-291518 is higher at 2-weeks than at 4-weeks.

It is important to distinguish between this lesion and those caused by marimastat in rats. Growth plate thickening was indeed seen with marim., but it also caused subphysal fracture, fibroplasia of soft connective tissue, particularly at the tendonis insertion and impaired mobility.... all of which were produced at lower trough concentrations than those necessary to produce the growth plate lesion for A-291518

Suffice it to say that A-291518's toxicity profile in rat is a substantial improvement over ABT-770.

Toxicity Studies						
14-Day Oral Studies in Monkeys						
Compound AUC ₀₋₁₂ (µg·h/mL) Day 0/Day 12	Dose mg/kg /day	Mortality Incidence	Weight Gain (kg) n/1	Bile Acids µmol/L	Stomach Necrosis Incidence	Other Histopathology (# affected/# examined)
ABT-770						
	0	0	+0.29/-0.01	4.6	0/10	None
115/344	30	0	-0.00/+0.06	7.1	0/6	None
220/550	100	0	-0.08/+0.14	12.3	4/6	None
433/1,060	300	4	-0.38/+0.26	28.1	9/10	Lung phospholipidosis (3/6)
A-291518						
	0	0	-/-0.07	2.9	0/2	None
620/159	100	0	+0.16/-0.10	10.7	0/2	None

✧ A-291518 does not produce the debilitation, lethality seen with ABT-770 in monkeys
 ✧ absence of phospholipidosis is consistent with minimal metabolites in tissues

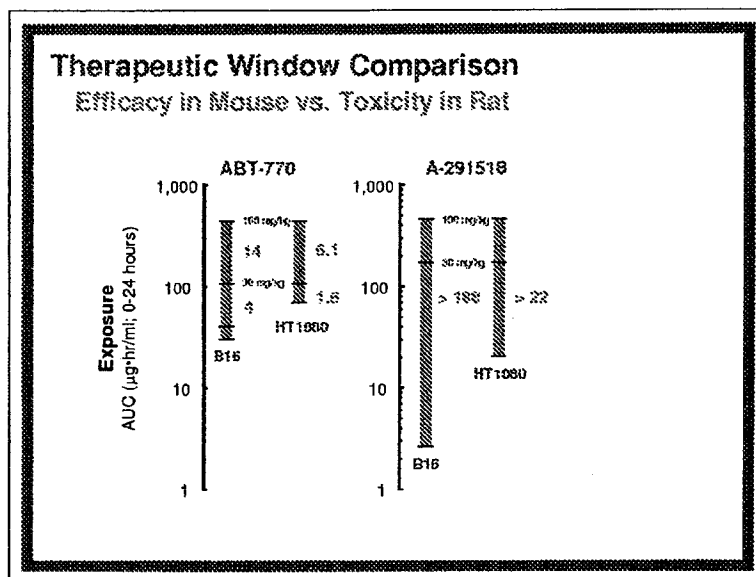
The effects of A-291518 given once daily doses of 100 mg/kg in monkeys over two week are compared to ABT-770 here.

Once again, ABT-770 produced lung phospholipidosis (perhaps related to the accumulation of metabolites), necrosis of the stomach epithelium, increase in bile acids, a reduction in weight gain and lethality.

None of these effects were observed with A-291518.

One factor to keep in mind here is that the A-291518 portion of this study involved only two treated and two control monkeys versus 6 or more for the ABT-770 study.

Now, independent of the fact that we did not identify an MTP for A-291518 in either the rat or the monkey study, we can begin to compare the therapeutic window between the two compounds on the next slide.



What I show here is a comparison of AUCs necessary to produce at least 30% inhibition of tumor growth in the B16 and HT1080 tumor models **RELATIVE** to the AUCs associated with maximum tolerated dose in 4-week rat toxicity studies.

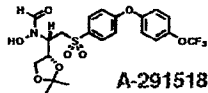
Admittedly this analysis crosses species and it is model dependent, yet we're really using this to compare 2 compounds.

ABT-770 did not clear the 100 mg/kg dose so its therapeutic window is somewhere between 4 and 14 for the B16 model and somewhere between 1.6 and 6.1 for the HT1080 model.

For A-291518, we don't really know how high the green bars go but its therapeutic window in both models (greater than 188 and greater than 22) are still substantially higher than ABT-770's.

Matrix Metalloproteinase Inhibitors Project

Summary & Goals



A-291518

A-291518 Attributes

- ❖ 200-fold greater gelatinase B potency than ABT-770
- ❖ > 100-fold greater gelatinase/fib. col. selectivity than prinomastat
- ❖ antitumor efficacy similar to ABT-770 and prinomastat
- ❖ metabolite burden less than ABT-770
- ❖ larger therapeutic window than ABT-770

Goals

- ❖ GLP synthesis of 4 kg A-291518 (6-00)
- ❖ single-dose Phase I study in healthy volunteers (10-00)
- ❖ multiple-dose Phase I study in cancer patients (3-01)

To conclude, think A-291518 is a compelling alternative to ABT-770 with the potential to be superior to competitor's compounds it being

- much more potent vs. gel B than ABT-770
- much more selective for gelA vs. fil. col. than prino
- yet have equivalent or superior antitumor efficacy
- a metabolite burden less than that of ABT-770 the

consequence being a greater therapeutic window.

Given the blessing of this esteemed body of scientists, our goals are

- the synthesis of 3 kg of material sometime in June
- Phase I single dose studies by October and
- multiple dose studies by this time next year

Matrix Metalloproteinase Inhibitors Project			
Acknowledgments			
Tox/Path	Chemotherapeutics	Pharmacokinetics/ Metabolism	NMR
Sherry Morgan	Juan Leal		Steve Festik
Bill Bracken	Karl Mollison		Phil Hajduk
Becky Gum	Debra Ferguson		Dave Nettlesheim
John Sullivan	Ruth Huang	Kennan Marsh	Ed Olejniczak
Lori Gallenberg	Ken Jarvis	Joy Bauch	Suzy Shuker
Mary Helgren	Christina Mareskes	Dean Hickman	Rob Meadows
Sali Tekeli	Jon Neubrook	Jim Schmidt	Dave Augeri
Dave Morfitt	Mike Milton	Stan Roberts	Dave Beisbenner
Pat Cusick	Nick Nickolaids	Bess Everitt	
Roger Ulrich	Mike Nukkala	Leah Anderson	
Reld Patterson	Andy Olekajew	Tony Borre	Molecular
Ken Majors	Lenette Paige	Hugh Nellans	Biology
Donna Davila	WeiGuo Qing	Shrish Raja	Happy Smith
Barry Fickbohm	Jason Stavropoulis	Ellen Roberts	Erol Gubbins
Jane Fagerland	Ann Tovclmak	George Nequist	Regina Reilly
Marilyn Diehl	Yi-Chan Wang		Bob Simmer
Ron Snyder	Jeff Alder	Safety Evaluation	
	Patty Ewing	Glenn Reinhart	Process
Pre-Formulations	Karamjeet Pandher	Lee Preusser	Research
Michelle Long	Sean Wilson	Sam Calzadilla	Steve Wittenberger
Gao Yi	Nicolela Zielinski	Brian Cox	Steve King
Eric Schmitt		Bill Giardina	Sou-Jen Chang
Jim Fort	Modeling/Probes		Ashok Gupta
	Charlie Hutchins	Legal	David Hill
	Jonathan Greer	Greg Steele	Dilnile Fernando
	Paul Richardson	Greg Donner	
		Patn Mingo	

Before I give way to Lisa Lux for the commercial assessment, I'd like to acknowledge some of the many participants in the MMPI effort....

Sherry Morgan, Bill Bracken and Becky Gum from Tox/Path

Michelle Long

Juan Leal & Karl Mollison

Kennan, Joy, Dean and Jim

Steve Wittenberger

Matrix Metalloproteinase Inhibitors Project			
Acknowledgments			
Current MMPI Project Team	Current MMPI Project Team	Former MMPI Project Team	Special Consultants
Dan Albert	Abdullah Kherzai	George Carrera	Perry Nisen
Jennifer Bouska	Junling Li	Rick Conway	Saul Rosenberg
Mike Curtin	Terry Magoc	Rick Craig	Jack Henkin
Yujia Dai	Pat Marcotte	Joe Dellaria	Hing Sham
Idiko Elmore	Mike Michaelides	Mike Falduto	Vince Giranda
Robin Frey	Doug Morgan	Alan Florjancic	Rick Lesniewski
Bob Garland	Shannon Murphy	Jane Gong	George Carter
Keith Glaser	Lori Pease	Zhiwen Guan	Shing Chang
Carole Goodfellow	Jamie Stacey	Gongjin Luo	
Yan Guo	Mike Staver	George Sheppard	
Robin Heyman	Doug Steinman	Jim Summers	
Jim Holms	Paul Tapang	Lianhong Xu	
	Carol Wada		

Listed here are the current and former members of D47J... these are a truly formidable group of drug discoverers.... please stand.

Some of these former members just didn't cut it.....

Special Consultant have been "AWESOME"

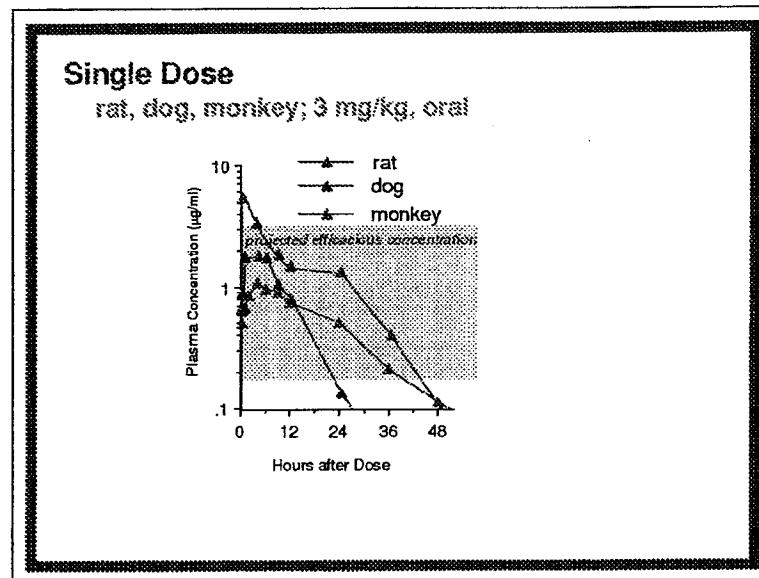
<p>Status of Competition</p> <p>Marimastat</p> <p><u>Phase III - non-resectable pancreatic cancer</u></p> <ul style="list-style-type: none"> ❖ marimastat versus gemcitabine (414 patients; marimastat 5, 10, 25 mg, bid) <ul style="list-style-type: none"> - survival no better for marimastat (25 mg) than gemcitabine ❖ marimastat plus gemcitabine (239 patients; marimastat 10 mg, bid) <ul style="list-style-type: none"> - no difference in survival - trend for better response in patients with less extensive disease <p><u>Phase III - inoperable gastric cancer</u></p> <ul style="list-style-type: none"> ❖ 369 patients; marimastat 10 mg, bid vs. placebo; cut-off = 85% mortality ❖ 1st cut-off: 14.1% placebo patients alive 22.7% marimastat patients alive ($p = 0.084$) ❖ 2nd cut-off: 25 of 35 survivors marimastat treated ❖ significant benefit in patients without metastasis at 1st cut-off ($p = 0.033$) ❖ BBT/Schering pursuing accelerated approval in gastric cancer <p><u>Current studies</u></p> <ul style="list-style-type: none"> ❖ glioblastoma, ovarian, SCLC, NSCLC, breast,

Results from Phase III studies with marimastat shed some light on how we might design of our clinical trials since they suggest that MMPI might be more beneficial to patients with earlier stage of disease.

As you know, pancreatic cancer is a highly aggressive cancer which progresses very quickly. When dosed head to head or in combination with gemcitabine, marimastat failed to produce a significant enhancement in survival relative gemcitabine alone. There was, however, a trend for a better response in patients with less extensive disease was observed.

More encouraging results comes from a study of marm. given to gastric cancer patients... a 10 mg, bid dose producing statistically significant increase in survival among the 101 who were enrolled without evidence of metastasis. Again, consistent with the idea that MMPIs may be most beneficial in earlier stage of disease.

I will be quite interesting to see if these trends are borne out when results from several Phase III studies are reported in the next 9 months.



some MMPs more important than others.... therefore which to inhibit and which to spare?

<p>Status of Competition</p> <p>BAY 12-9566 (tanomastat) - Bayer</p> <p><u>Project Team findings</u></p> <ul style="list-style-type: none"> ❖ modest MMP potency (gel A IC₅₀ = 120 nM, gel B IC₅₀ = 1,600 nM) ❖ lacks activity in cancer animal models ❖ long half-life; > 99.9% protein bound <p><u>Phase III - small cell lung cancer (following best therapy)</u></p> <ul style="list-style-type: none"> ❖ interim analysis of 200 patients (800 mg, bid over 18 months) <ul style="list-style-type: none"> - greater disease progression among treated patients vs. placebo - 30% difference in survival rate ❖ BAY 12-9566 withdrawn from all trials as "precautionary measure" ❖ causes? <ul style="list-style-type: none"> - no toxicity observed in extended Phase I studies
--

Tanomastat was the name given to BAY 12-9566 from Bayer.....In our hands, this compound is only modestly potent (120 & 1,600nM), lacks in vivo effects and is highly protein bound.

Until recently BAY 12-9566 was in development for both cancer and arthritis, however interim analysis of a Phase III trial of in SCLC patients indicated greater disease progression and higher mortality among treated patients versus placebo
CONSEQUENTLY Bayer has withdrawl BAY-129566 from all trials as precaution.

We do not interpret this as a negative for the idea of MMP inhibition to treat cancer. that's based on

- BAY 12-9566 is less potent and more selective than marimastat and that
- marimastat has been in been given to lung cancer patients as long as BAY

The cause for enhanced progression are not obvious, especially since BAY 12-9566 exhibited no significant toxicity in extened Phase I studies.

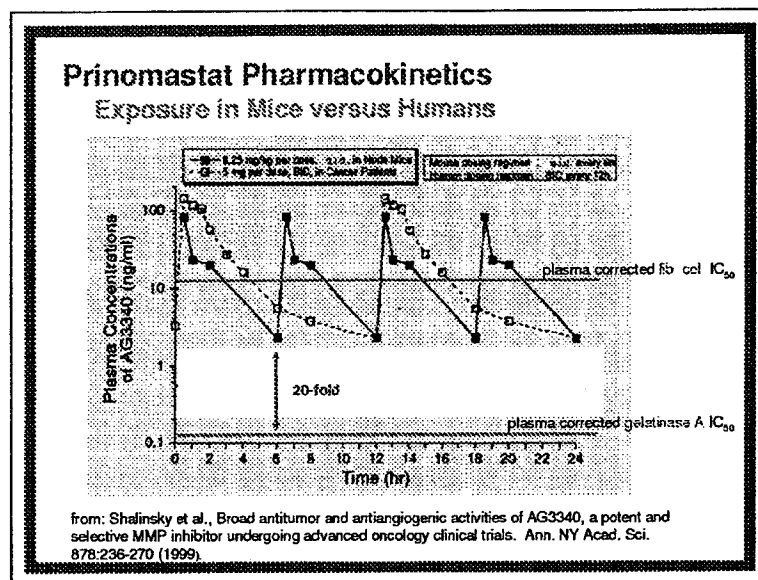
We gone back and pulled the papers investigating the expression of MMPs in SCLC and, interestingly, of all the cancers in which MMP expression has been examined, SCLC is one of the few example where gelatinase A expression is not detected in biopies. Now, this may explain why it didn't work, but it doesn't explain the enhanced progression.

<p>Status of Competition</p> <p>Agouron, Bristol-Myers Squibb</p> <p><u>Prinomastat - Agouron/Warnar-Lambert/Pfizer</u></p> <ul style="list-style-type: none"> ◇ "too many complaints about joint effects at 25 mg, bid" <ul style="list-style-type: none"> - current studies restricted to 15 mg, bid and lower ◇ Phase III studies (NSCLC, prostate cancer) to assess combination therapy <p><u>BMS 275291 - Bristol-Myers Squibb/Chirosciences</u></p> <ul style="list-style-type: none"> ◇ broad MMP inhibition, no TACE activity ◇ does not cause lesions in marmoset model of joint toxicity ◇ multiple-dose Phase I trial (cancer patients; 600 - 2,400 mg/day, 4-weeks+) <ul style="list-style-type: none"> - grade 1 myalgia/arthralgia in 7 of 28 pateints - grade 2 myalgia/arthralgia in 3 of 28 pateints - reversible skin rash

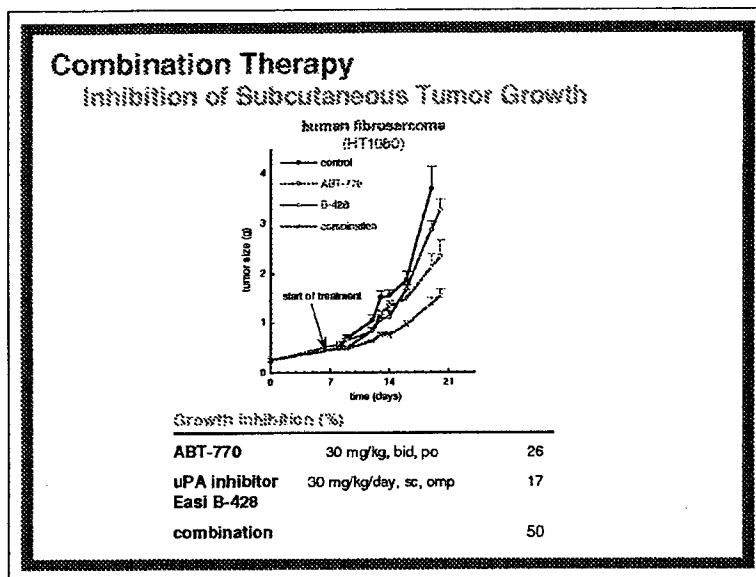
As with marimastat, the clinical evaluation of prinomastat is hampered by dose-limiting joint effects - to quote one of their scientists at a recent meeting they received "too many complaints about joint effects coming from patients @ 25 mg bid" consequently all their Phase III studies will cover doses not exceeding 15 mg, bid.

Those Phase III studies are being conducted on NSCLC and prostate cancer patients in combination with standard cyptotoxic drugs - results from both studies should be out this year.

We talked about the BMS compound - grade 1 and grade 2 myalgia/arthralgia being observed in Phase I multi-dose studies. This compound also produces a reversible skin rash similar to what was seen with a previous Novartis compound.



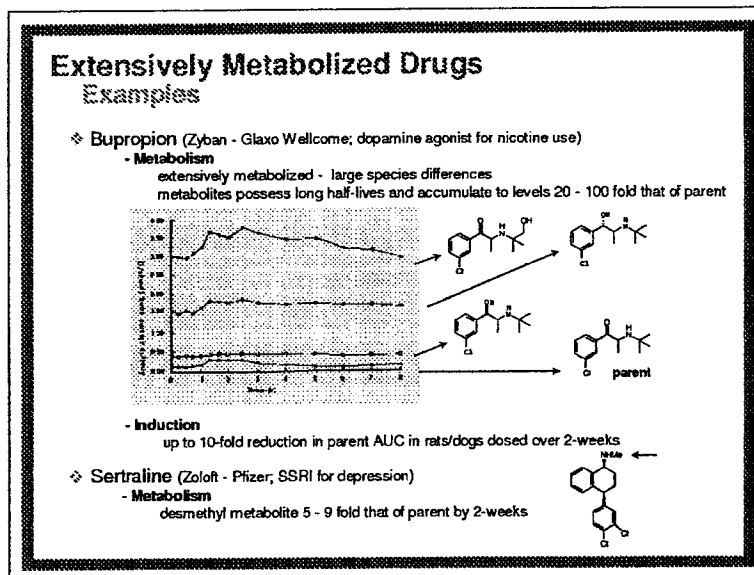
some MMPs more important than others.... therefore which to inhibit and which to spare?



Shown here is the effect of A-291518 on tumor growth in three models given as

- single agent (green)
- cytotoxic agent given as a single agent (blue)
- A-291518 plus cytotoxic agent (red)

in each case, combination therapy producing greater growth suppression than either agent dosed alone.



Listed here are the current and former members of D47J... these are a truly formidable group of drug discoverers.... please stand.

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Comparison of Therapeutic Windows

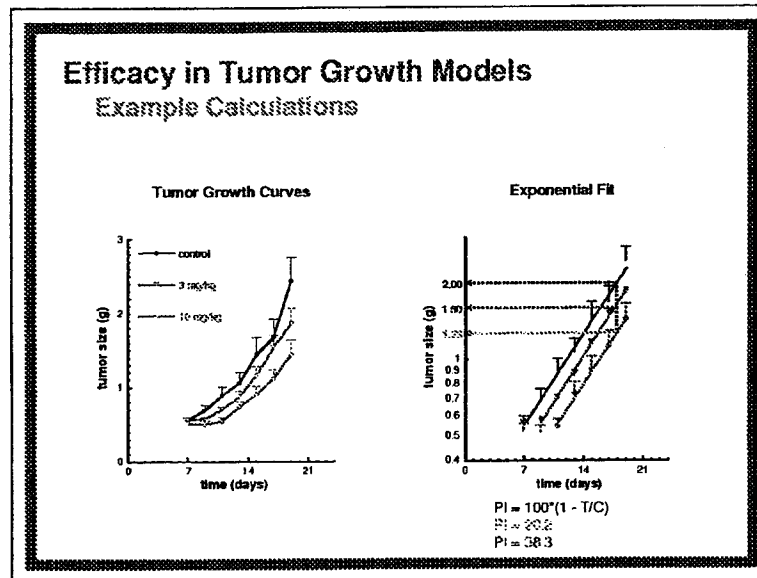
Efficacy in Mouse versus Toxicity in Rat & Monkey

Inhibitor model	Efficacy			Safety							
				4-week rat				2-week monkey			
	dose bid	PI	AUC	dose qd	AUC	therapeutic ratio B16	HT1080	dose qd	AUC	therapeutic ratio B16	HT1080
ABT-770	6	38	30	10	40	1	0.6	30	344	11	5
B16				30	115	4	1.6	100	590	18	8
HT1080	60	25	70	100	429	14	6.1	300	1060	35	15
A-291518	6	33	2.6	30	185	71	8	100	159	61	7
B16	20	38	22	100	488	188	22				
HT1080											

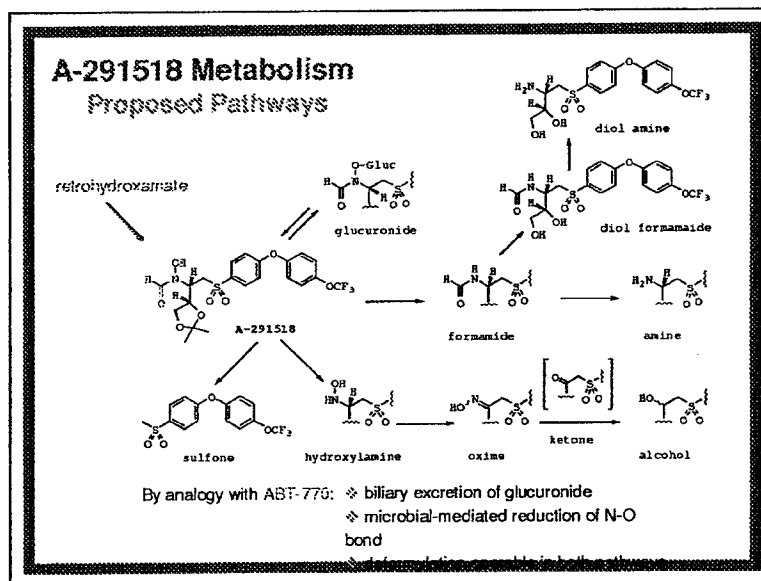
Compounds are efficacious when dosed in combination with cytotoxic agents....
Shown here are the effects of ABT-770, A-291518 & A-316023 on tumor growth in this B16 flank model given as a

- single agent
- paclitaxel given as a single agent
- MMPI plus paclitaxel

This additional effect is not as apparent with ABT-770 & A-316023 since this % inhibition is measured at 2 grams... yet I think you can see an effect in each case.



some MMPs more important than others.... therefore which to inhibit and which to spare?



We have studied the metabolism of ABT-770 both in vitro and using ^{13}C -labeled material in rats and have constructed the following metabolite pathway.

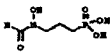
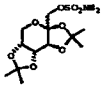
Bile duct cannulation studies suggest that the metabolite degradation of ABT-770 is initiated by biliary elimination of its glucuronide.

Once in the gut the N-O bond of ABT-770 is reduced giving the formamide. This is likely mediated by intestinal bacteria since incubation of ABT-770 with rat intestinal contents under anaerobic conditions gives rise to the formamide. The formamide is converted to the amine by liver microsomes.

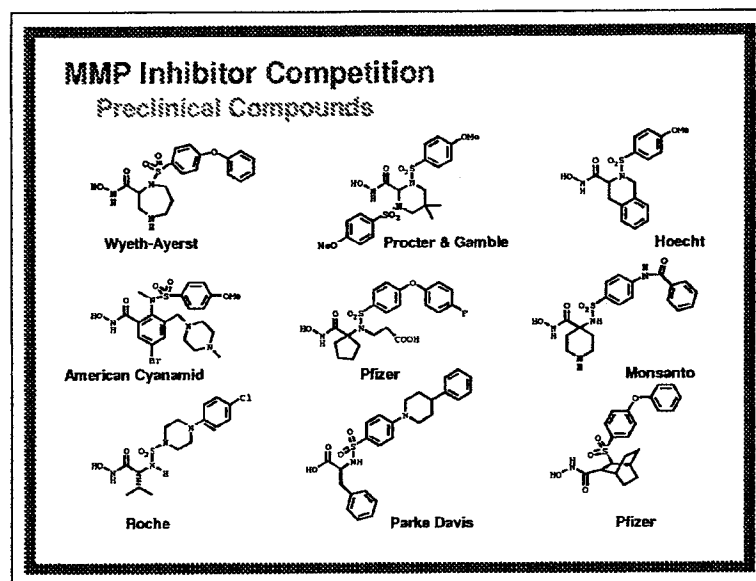
The same deformylation initiates another pathway which ultimately produces the alcohol via the mixture of oximes shown here.

Important to recognize that all metabolites are produced by transformation of retrohydroxamate moiety which chelates zinc at active site of MMPs so none possess MMPI inhibitory activity.

This is for ABT-770, what about the backups?

Retrohydroxamates and Acetonides	
Clinical Examples	
 <p>Fosmidomycin</p>	<ul style="list-style-type: none"> • through Phase II • well tolerated 8 g/day iv 7 days, 4 g/day po 7 days • serum half-life 1.7 h • no serum accumulation, 2 g 4x/day for 7 days
 <p>Topamax (Topiramate) Ortho-McNeil</p>	<ul style="list-style-type: none"> • anti-epileptic • F > 80% • elimination half-life 21.5 h • hydrolysis metabolite <5%

some MMPs more important than others.... therefore which to inhibit and which to spare?



some MMPs more important than others.... therefore which to inhibit and which to spare?

Gender-Dependent Xenobiotic Metabolism

Differences Between Species

Rodents

- ❖ Gender-dependent metabolism well established in rodents
 - large differences in expression of certain CYP450s....
 - expression of CYP3A2 is 10-fold higher in males rats than females
 - expression of CYP2C12 is 20-fold higher in females rats than male

Humans

- ❖ Differences in CYP isozyme expression not as large in humans AND differences are not the same as in rodents (CYP2D6 M>F; CYP3A4 F>M)
- ❖ Studies of gender-dependent metabolism in humans must consider hormonal changes due to
 - physiology (menstrual cycle, pregnancy, menopause)
 - pharmacology (contraceptive use, smoking, alcohol...)
- ❖ When these factors are considered, processing of phenotyping probes not substantially different between males and females

some MMPs more important than others.... therefore which to inhibit and which to spare?

Gelatinase B-Deficient Mice
Role for Gelatinase B In Angiogenesis

Phenotype

- abnormal patterns of skeletal growth plate vascularization/ossification (tibia, femur, metatarsal)
- delay in ossification leads to growth plate thickening
- 10% shorter long bones when mature, otherwise developmentally normal
- lesion rescued by bone marrow transplantation
- lesion resolves over 8-weeks after birth (growth plates close)

❖ gelatinase B functions in ossification and vascularization during development via controlling angiogenesis

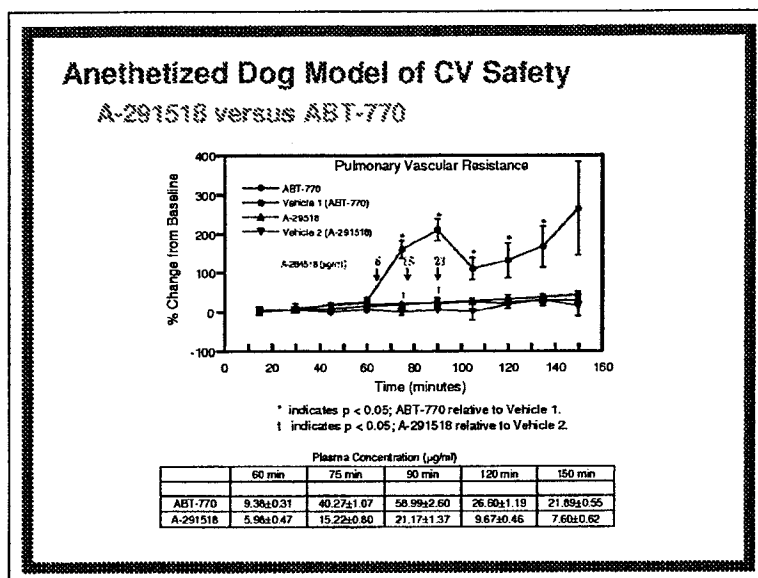
some MMPs more important than others.... therefore which to inhibit and which to spare?

CYP450 Induction/Inhibition		
Preliminary Experiments		
❖ Western blotting for cytochrome P450 isozymes in whole cell extracts from A-291518 and vehicle-treated rats & monkeys		
rat/monkey isozyme	fold-change versus vehicle control	
	monkey	rat
CYP3A	none	2 (males); 8 (females)
CYP2B	none	2-4 (males)
CYP1A	none	none
CYP2C	none	none
❖ Inhibition of human cytochrome P450 isozymes		
human isozyme	IC ₅₀ (μM)	
CYP3A1	2 - 25	
CYP2C9	> 25	
CYP1A2	> 25	

some MMPs more important than others.... therefore which to inhibit and which to spare?

A-291518 <i>In Vitro</i> Metabolism		
Preliminary Experiments		
❖ Metabolites formed following incubation with liver microsomes		
substrate	microsomes plus NADPH	
	human	rat
A-291518	none	none
A-291518- formamide	amine & formamide diol	amine & formamide diol
A-291518- sulfone	none	none
❖ Experiments using hepatocytes and liver slices to follow		

some MMPs more important than others.... therefore which to inhibit and which to spare?



some MMPs more important than others.... therefore which to inhibit and which to spare?

Modeling Joint Toxicity

Issues with Preclinical Studies

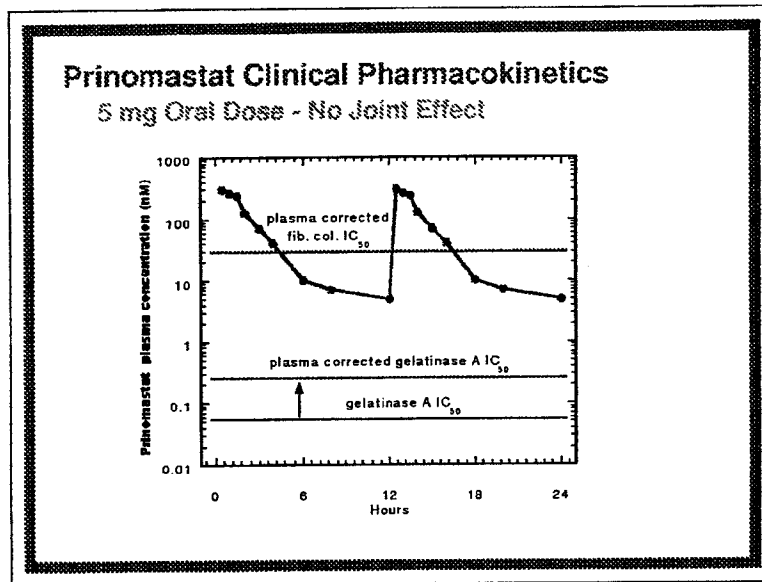
Abbott Studies

- ❖ marmosets dosed with marimastat (200 mg/kg/day, po, 28 days)
 - markedly reduced mobility
 - tendon thickening & fibrosis, mild inflammation
- ❖ rats dosed with marimastat (OMP; $C_{ss} = 500$ nM; 2 weeks)
 - growth plate thickening & fracture, fibroplasia of synovium, tendinous insertion
 - impaired mobility
- ❖ rats dosed with A-291518 (30 mg/kg/day, po, 28 days; trough > 1 μ M)
 - thickening of growth plate
 - reduce incidence at 4-weeks versus 2-weeks

Published Data

- ❖ BMS-275291 was VOID of joint effects in marmosets; produces arthralgia clinically
- ❖ collagen turnover is mediated by enzymes other than tib. coll. in rodents
- ❖ thickening of growth plate seen in gelatinase B-deficient mice
 - resolves after 3 weeks

- ❖ validated models of MMP-induced joint toxicity do not exist
- ❖ assessment of A-291518 joint effects will require Phase I multiple-dose studies



some MMPs more important than others.... therefore which to inhibit and which to spare?

Why Target the Gelatinases?
Role of Gelatinases in Tumor Progression

- ❖ gelatinases most consistently associated with tumor progression
- ❖ substrate specificity of gelatinases (type IV collagen) allows tumor cells to penetrate basement membranes
- ❖ gelatinase A and B can localize to the site of tumor invasion via binding surface associated proteins
- ❖ gelatinase A-deficient mice develop normally, but exhibit suppression of tumor growth and metastasis
- ❖ experimental metastasis is suppressed in gelatinase B-deficient mice
- ❖ gelatinase B-deficient mice crossed with Rip Tag mice results in reduced tumor burden in off-spring

First, relative to other MMPs, the gelatinases are most consistently associated with tumor progression based on biopsies from a # of different tumor types.

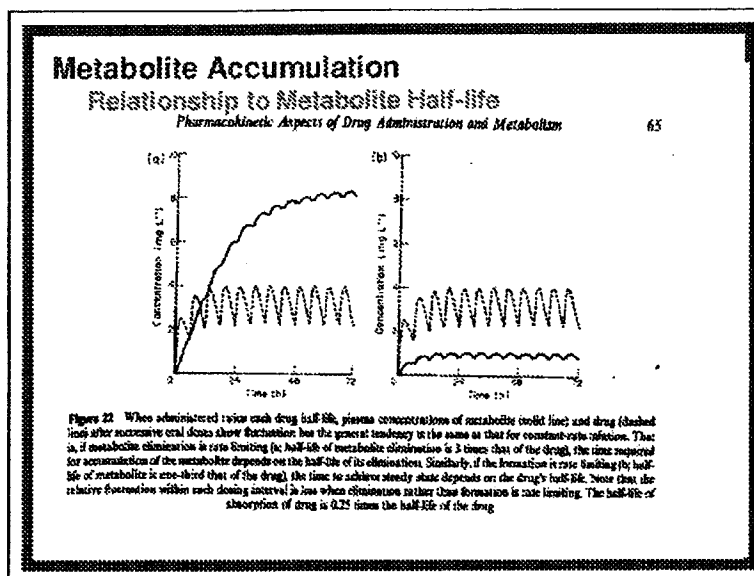
in order for tumor cells to enter vasculature, must degrade basement membranes. Type IV col. is major componenet of base. mem. and good substrate for the gels.

Gel A&B have unique ability to localize to leading egde of invading tumor cells by binding surface associated proteins....

Tumor cells implanted in gel A KO mice grow more slowly and metastasize less readily than normals....

Finally, when gel B KO mice are crossed with a stain of mice predisposed to forming pancreatic cancinomas, see a significant reduction of tumor burden in off-spring.

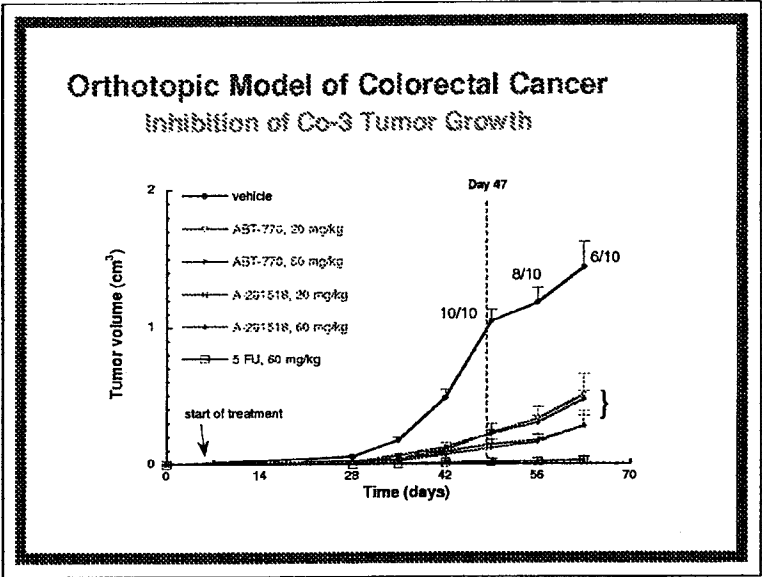
Based on this evidence, we'd like our compounds to inhibit the gelatinases.... BUT we'd also like to avoid broad MMP inhibition and the reason for that relates to the side effect profile of broad spectrum inhibitors currently in clinical trials...



Phospholipidosis	
Relevance to MMP Inhibitors	
Definition:	phospholipid storage disorder accumulation of phospholipids in cell lysosomes
Mechanism:	altered phospholipid trafficking inhibition of phospholipid catabolism
Cause:	commonly cationic amphiphilic drugs amiodarone, chlorpheniramine, imipramine chlorpromazine, tamoxifen, gentamicin
Susceptibility:	high in rodents, wide species variations
Correlations:	appears to correlate with accumulation of drug cell culture assay useful predictor not necessarily relevant to any particular toxicity

Phospholipidosis**Induction in Hepatocytes**

	Rat	Human
ABT-770	-	-
formamide	+/-	+/-
amine	++++	++++
A-291518	-	-
formamide	-	+/-
amine	+/-	+/-
oxime	+/-	ND
A-316023	-	-
formamide	+/-	+/-
amine	+++	+++



Estimating Target Trough Concentrations Based on Marimastat Studies

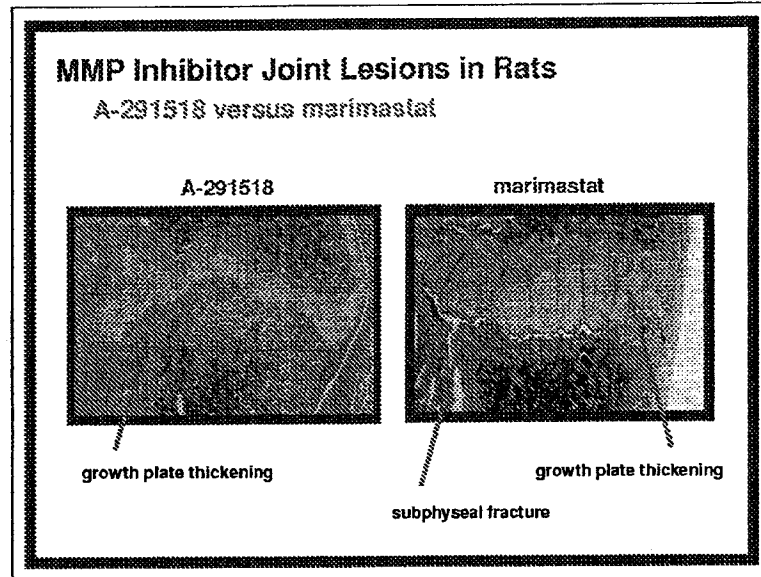
marimastat

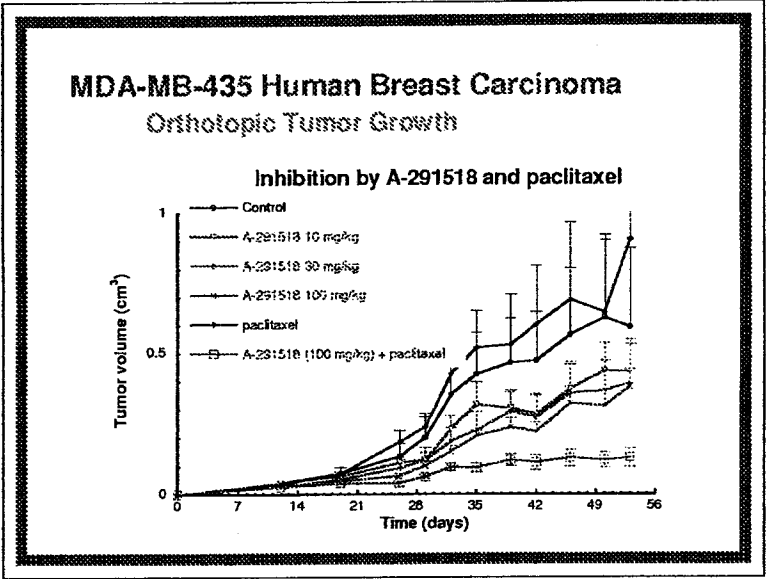
- ❖ 10 mg, bid "efficacious" in gastric cancer trial
- ❖ trough concentration of marimastat (10 mg, bid) across multiple trials ~ 50 µg/L = 150 nM
- ❖ mean gel A/gel B IC_{50} = 0.6 nM
- ❖ plasma shift = 3-fold
- ❖ plasma corrected gel IC_{50} = 1.8 nM..... 150/1.8 ~ 83
- ❖ ∴ "efficacious" trough concentration = ~ 83-fold greater than plasma corrected mean gel A/gel B IC_{50}

A-291518

- ❖ mean gel A/gel B IC_{50} = 0.65 nM
- ❖ plasma shift = 53-fold
- ❖ plasma corrected gel IC_{50} = 35 nM
- ❖ ∴ "efficacious" trough concentration 83 x 35 nM ~ 3 µM

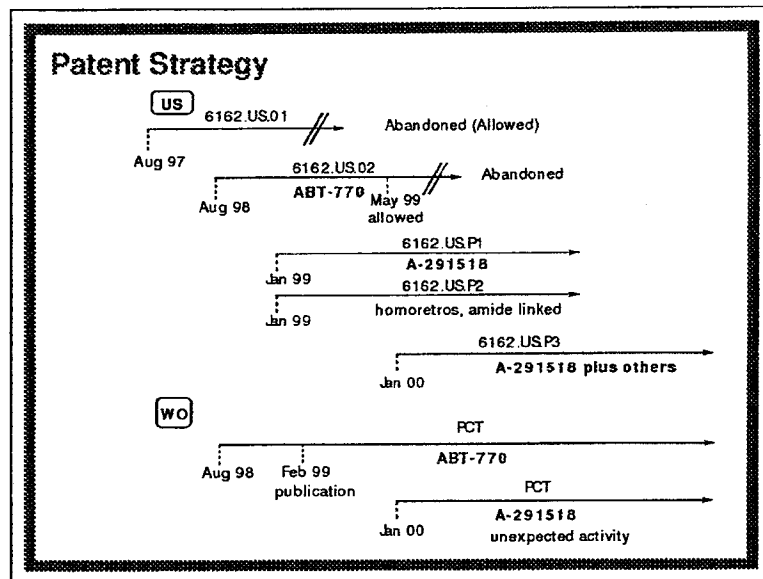
some MMPs more important than others.... therefore which to inhibit and which to spare?





MDA-435 Human Breast Carcinoma Metastases				
Effect of A-291518 on Axillary Lymph Node Weight				
	Mean Weights (mg, +/- SEM)			% Inhibition
	Lateral	Contralateral	Metastases	
Control (vehicle)	20.47 +/- 2.45	11.27 +/- 1.22	9.20 +/- 2.51	
200 mg/kg	12.50 +/- 1.05	9.89 +/- 1.01	2.83 +/- 1.59	69
60 mg/kg	11.11 +/- 1.34	8.26 +/- 1.28	2.85 +/- 1.45	69
20 mg/kg	11.19 +/- 1.51	8.29 +/- 1.10	2.90 +/- 1.25	69

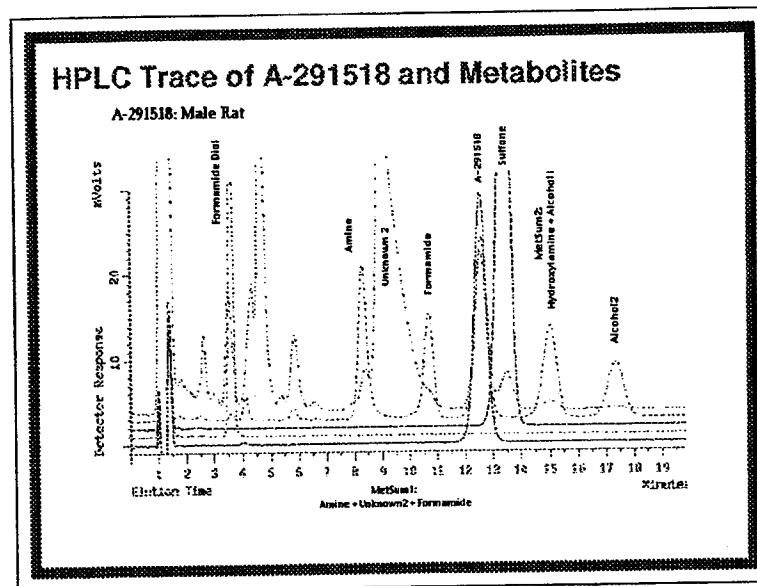
some MMPs more important than others.... therefore which to inhibit and which to spare?



some MMPs more important than others.... therefore which to inhibit and which to spare?

MMP-deficient Mice Various Phenotypes	
MMP-deficiency	Observed phenotype
gelatinase A (MMP-2)	reduced angiogenesis and tumor progression
gelatinase B (MMP-9)	delayed angiogenesis in bone growth plate, plus
stromelysin-1 (MMP-3)	no different in collagen-induced arthritis model
matrilysin (MMP-7)	decreased intestinal tumorigenesis in MIN mouse
stromelysin-3 (MMP-11)	decreased chemical-induced tumorigenesis
matrilysin-2 (MMP-12)	protection from cigarette smoke-induced emphysema
MT1-MMP (MMP-14)	skeletal abnormalities, fibrosis of soft tissue, arthritis
♦ knockout of individual MMPs generally well tolerated - few effects on development ♦ MT1-MMP knockout appears to mimic marimastat-induced joint effects "wherever collagen turnover is important, MT1-MMP KO mice have defects"	

some MMPs more important than others.... therefore which to inhibit and which to spare?



some MMPs more important than others.... therefore which to inhibit and which to spare?

Deposition Exhibit No. 3

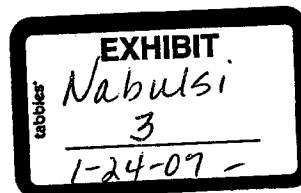
P's Exhibit E

ABT-518

TRANSITION STRATEGY

(MMPI)

August 2000



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ABBT0092083

ABT-518 Transition Strategy
August 2000

ABT-518 TRANSITION STRATEGY

1. Introduction and Background

For most cancers, the level of physician satisfaction with current therapies is low given the highly toxic nature of the treatments. A new avenue being investigated is the use of "cytostatic" agents. This approach to therapy has the potential to transform cancer into a chronic disease that patients live with long-term, much like the effect protease inhibitor therapy has had on patients with HIV infection. Abbott's matrix metalloproteinase inhibitor (MMPI) program is one example of this novel therapy with the potential to alter the way cancer is treated by preventing or modifying disease progression and/or metastases.

The MMPs comprise a family of enzymes that degrade a wide range of tissue matrix protein substrates. Many solid tumors have high expression of these enzymes and this is associated with the ability of tumors to aggressively grow, invade, develop new blood vessels and metastasize. Experimental evidence suggests that the MMPs gelatinase A and gelatinase B are particularly important in tumor progression. The Discovery Project Team has therefore targeted gelatinase selective inhibitors for the treatment of cancer. Another reason for targeting highly gelatinase selective MMP inhibitors relates to the side effect profile exhibited by broad-spectrum agents like marimastat. Chronic administration of marimastat causes severe joint pain and stiffness that precludes the use of high doses in clinical trials. The joint-related adverse events are believed to be related to the inhibition of other MMPs, namely MMP-1 (fibroblast collagenase).

ABT-518, a member of Abbott's biaryl ether retrohydroxamate series of inhibitors, replaced ABT-770 as the lead MMPI transition candidate. Preclinical toxicity studies with ABT-770, Abbott's first MMP inhibitor development candidate, revealed a number of adverse effects which occurred at drug exposures only several fold higher than that necessary for efficacy in animal models. The MMP selectivity and potency profile exhibited by ABT-518 distinguish it from ABT-770 and the competitor's compounds. ABT-518 possesses sub-nanomolar potency versus gelatinase B, an improvement of 200-fold over ABT-770. ABT-518 is also a substantially more selective inhibitor of the gelatinases compared to prinomastat, suggesting that it may avoid mechanism-based joint effects.

In animal tumor models, ABT-518 demonstrated anti-tumor activity equal or superior to ABT-770 and prinomastat. Inhibition of tumor growth was dose dependent in both syngeneic and xenograft models. Infusion studies with osmotic minipumps designed to determine the minimal blood levels necessary for efficacy showed that steady-state blood levels of ABT-518 ranging from 0.13 µg/ml (B-16 syngeneic melanoma) to 0.57 µg/ml (HT1080 human fibrosarcoma) resulted in biologically significant inhibition (defined as ≥ 30% inhibition of tumor growth over that of control). Comparable efficacy via the oral route was achieved with doses, given twice a day, of 3 and 10 mg/kg, respectively, in the two experimental models. These doses would be roughly 200-800 mg in humans. ABT-518 was also effective in blocking blood vessel formation in a mouse ocular model of angiogenesis.

ABT-518 gave sustained plasma concentrations following single oral dosing in monkeys, dogs and rats. Bioavailability ranged between 68 and 93% depending on formulation and species. Multiple metabolites are produced after repeated oral dosing, some reaching plasma concentrations in excess of

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ABBT0092084

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parent drug. Most of the metabolites result from modification of the retrohydroxamate moiety, although the relative amounts vary with gender and species. Plasma concentrations will be assessed in Phase I to determine safety margins and potential drug-drug interactions.

The preclinical safety profile exhibited by ABT-518 is more favorable than ABT-770. ABT-518 displays no significant effects in screening studies for genotoxicity, cytotoxicity and ligand binding assays and its cardiovascular effects in dogs are unremarkable. Toxicity studies in rats and monkeys (non-GLP) reveal none of the debilitation and lethality seen with ABT-770. Tissues from these animals reveal no evidence of phospholipidosis which likely reflects the reduced tissue burden of metabolites produced by ABT-518 relative to ABT-770. Plasma concentrations generated by ABT-518 in rat toxicity studies are at least 20-fold higher than that necessary to produce efficacy in animal tumor models.

Several orally bioavailable MMP inhibitors are being assessed in phase II/III clinical trials for the treatment of cancer (Table 1). Preliminary results from several trials suggest that treatment with an MMPI can cause disease stabilization. Results from Phase III studies with marimastat have been both positive (gastric cancer) and negative (pancreatic cancer and glioma) and suggest that MMP inhibitors are more likely to benefit patients at earlier stages of disease progression. A survival benefit for marimastat was seen in 101 inoperable gastric cancer patients without metastases ($p=0.033$). However, all but tanomastat report dose-limiting side-effects characterized by pain and stiffness of the joints (BMS-275291 showed Grade 1/2 joint effects). Although tanomastat is highly gelatinase selective, it exhibits only marginal to modest potency against MMP-2. The incidence of joint toxicity exhibited by marimastat, prinomastat, and BMS-275291 may negatively influence the likelihood of their ability to demonstrate efficacy in Phase II/III studies. Doses of 5, 10 and 25 mg administered BID were chosen for the Phase III trials for marimastat. These are below the dose at which joint toxicity was observed in Phase I. Seven other randomized pivotal trials with marimastat are currently ongoing in SCLC, NSCLC, breast cancer, ovarian cancer, and in glioblastoma. Pfizer announced on 8/4/00 that Phase III clinical trials of prinomastat in patients with advanced non-small cell lung cancer (NSCLC) (in combination with paclitaxel/carboplatin and with gemcitabine/cisplatin) and in advanced hormone-refractory prostate cancer patients (in combination with mitoxantrone/prednisone) have been discontinued. The reason given was that "primary efficacy objectives were not met". Both studies assessed the effect of prinomastat at doses of 5, 10, and 15 mg BID. These dose levels are below the doses at which joint pain was observed in Phase I. They are continuing trials in less advanced tumors, e.g., esophagus, melanoma, breast, glioma, and NSCLC and will start trials in two additional tumor types.

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Table 1. MMP Inhibitors in Advanced Clinical Development

MMP Inhibitor Company	Development Stage	Tumor Type	Metalloproteinase Selectivity	Joint Toxicity
Marimastat British Biotech/ Schering	Phase III	NSCLC SCLC breast ovarian	Broad spectrum	yes
Prinomastat Agouron/ Pfizer	Phase III	esophagus melanoma breast glioma NSCLC* Prostate*	Moderately gelatinase selective	yes
BMS-275291 BMS/Chirosciences	Phase I/II	unknown	Broad spectrum; no TACE	yes
Tanomastat [†] Bayer	Phase III	SCLC NSCLC ovarian pancreatic	Highly gelatinase selective	No
ABT-518 Abbott Labs	Preclinical		Highly gelatinase Selective	TBD

* Discontinued in advanced disease. NSCLC continues in less advanced disease.

[†] Tanomastat (BAY12-9566) was discontinued from clinical development when an interim analysis of a study revealed increased mortality in the drug treated group. However, subsequent analysis of additional patients showed drug benefit and Bayer may resume clinical development (personal communication).

While the competition in the MMP inhibitor field is intense, no compound has yet been approved. The selectivity of ABT-518 suggests that it may be spared the dose-limiting joint toxicity observed with marimastat and prinomastat, thus expanding the range of tolerated doses and enhancing the likelihood of demonstrating clinical efficacy. ABT-518 is therefore a compelling successor to ABT-770 with the potential to demonstrate antitumor effects superior to the MMP inhibitors currently undergoing clinical trials.

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2. Transition Strategy

2.1. Objectives/attributes

The primary objective of the transition process will be to assess key attributes of ABT-518 that would justify a recommendation for full development or program discontinuation. Key desirable attributes for ABT-518 include:

- Acceptable animal toxicity profile following prolonged administration (one-month in two species).
- Favorable systemic exposure (0.1 µg/ml trough concentration) in cancer patients after oral administration not more than twice a day.
- Acceptable safety profile in cancer patients following a minimum treatment of one month.

The development activities during the transition period will be limited to two Phase I studies (a first-in-man multiple-escalating dose study ex-US and a small IND study), and the toxicology, metabolism and formulation activities needed to support Phase I activities. It is not the objective of the transition program to demonstrate proof of efficacy for this compound, as this can only be assessed during properly controlled studies.

Several Go/No Go decision points have been incorporated into the transition program, which has an overall objective of making a timely recommendation for the continuation of ABT-518 development or program discontinuation. The key Go/No-Go points are related to (1) preclinical toxicity (Sep 2000), and (2) safety and pharmacokinetics in patients from the multiple-dose study (Dec 2001). Throughout the transition, attention will be paid to the competitive environment by tracking the progress of other MMPs in development.

2.2. Key Issues/Risk Assessment

While several issues are expected throughout the development of a new class of cancer compounds, there are some key issues and risks specific to ABT-518 to be addressed during the transition period:

2.2.1. Formulation/Drug Supplies

Nominal drug formulation work will be done during the transition stage of development. Preliminary work has shown that drug substance in a capsule, when taken with food, will provide an adequate PK profile but larger doses may be required. The lack of formulation optimization during transition will contribute to a 6-8 month gap prior to the start of Phase II.

2.2.2 Toxicology

The safety profile will need to be conducive to chronic administration in cancer patients. In screening studies, ABT-518 did not exhibit significant effects in genotoxicity, clastogenicity, cytotoxicity and ligand binding assays. In animal models, no significant CNS effects were produced by ABT-518 and the compound exhibited an improved acute cardiovascular safety profile relative to ABT-770. ABT-

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518 was well tolerated in rats treated for up to four weeks and in a small number of monkeys treated for two weeks. The maximum tolerated dose in both species was greater than the highest dose tested (100 mg/kg/day). Changes produced by ABT-518 included an increase in liver weight in rats and a slight decrease in food intake in one of two monkeys tested. No joint toxicity has been observed in either rats or monkeys. However, hypertrophy seen in the growth plates of rats needs further assessment. This hypertrophy is not believed to be similar to that reported with marimastat (subphyseal fractures, fibroplasia of the musculotendinous insertion sites, and clinically evident impairment of motion) and is seen in Gel B knockout mice without resulting deformities. Based on AUC values from preclinical efficacy and safety studies, ABT-518 has a larger therapeutic window than ABT-770 in rodents. In GLP toxicity studies it will be important to assess the occurrence of phospholipidosis as this was a significant finding with ABT-770.

The relationship of tissue metabolite accumulation to long-term safety is not known but is suspected to be important. Metabolites are produced following multiple oral doses of ABT-518 in rats and monkeys, with the absolute and relative amounts being gender and species dependent. However, accumulation of metabolites in tissues of treated rats and monkeys was far less for ABT-518 than for ABT-770. Five major metabolites of ABT-518 (selected by concentration and potential reactivity) have been synthesized for analytical method development. The toxicology program will include an assessment of metabolite production and toxicity. These metabolites will also be analyzed in the Phase I study. Analysis of this many metabolites is not a trivial undertaking and it is hoped that this number can be reduced once the human metabolite profile is better understood.

2.2.3. Clinical

The objective of the clinical program during Transition is to show that the safety and pharmacokinetic profile of ABT-518 in cancer patients are similar to or better than those of the competitor compounds. A prolonged exposure period will be required to assess the potential for joint toxicity in view of the MMPI competitor experiences. A secondary objective will be to establish a dose for the Phase II program.

Four critical questions need to be answered to recommend further development:

1. Can target trough plasma concentrations of 0.1 µg/ml be achieved after oral administration of ABT-518?
2. Can ABT-518 be administered once or twice a day?
3. Can ABT-518 be administered chronically in cancer patients with an acceptable safety profile?
4. Will ABT-518 produce the joint stiffness that has been observed with other MMPIs in development?

This transition assessment will not include a single-dose study in healthy volunteers. The primary reason for a normal volunteer Phase I single-dose study is to provide single-dose pharmacokinetics (PK), thus allowing the rapid selection of a starting dose for the Phase I multiple-dose study. This was true for ABT-839 (FTI) and ABT-510 (TSP). The questions that need to be answered for ABT-518 will require multiple dosing and are unlikely to be identified in a single-dose study. In addition, the competitor MMPI, marimastat, demonstrated differences in PK between normal volunteers and

*ABT-518 Transition Strategy
August 2000*

cancer patients, thus making it doubtful that the single-dose data would predict a starting dose in cancer patients.

However, if non-cancer indications are pursued, a Phase I SD/MD study in healthy volunteers may be required. Ophthalmologic indications such as macular degeneration or diabetic retinopathy would likely be topically dosed and would only require evidence of minimal systemic exposure. Indications requiring systemic exposure such as multiple sclerosis or rheumatoid arthritis would likely require additional Phase I studies in healthy volunteers.

It is known that joint toxicity is both compound-dependent and dose-dependent, and with broad spectrum MMPi's it has been seen only after four weeks of dosing or later. At lower doses it took more than eight weeks for the toxicity to be seen. While reports of joint toxicity during the initial portion (28 days) of the study are unlikely, this dose-limiting toxicity will be assessed during the extension portion of the study.

The planned multiple-dose study (and its extension) will establish ABT-518 pharmacokinetics in patients, and more importantly will assess the safety profile following a minimum of 28 days administration. The duration of the study and its extension will be sufficient to project the safety risks for chronic use of this class of cytostatic agent. The study objectives will be to:

- Identify the dose that will provide acceptable systemic exposure after oral administration (plasma trough concentrations of 0.1 µg/ml).
- Assess acute and multiple-dose safety.
- Identify potential doses for the Phase II program.

3. Transition Program

In order to achieve the above objectives and assess the ABT-518 specific attributes and issues, the Transition Team will carry out the activities described below:

3.1 Bulk Drug Synthesis

- 100 grams of non-GMP drug was delivered 12/99 by Chemical Sciences for selection of ABT-518 as a candidate.
- 1.7 kilograms of non-GMP material was delivered 6/00 for the one-month animal toxicity studies.
- 3.8 kilograms of GMP material was delivered 6/00 for the Phase I multiple-dose study.
- 10 kilograms of GMP material will be delivered 3Q01 to complete the Phase I trial with extensions and initiate Phase II preparation. This campaign might be larger depending on Chemical Sciences process initiatives.

3.2 Formulation Activities

- Available "drug in a capsule" data have demonstrated >63% bioavailability in fed dogs. Based on these data, the Transition Team will proceed into Phase I with drug substance in a capsule

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administered with food. Capsule strengths will be 25 mg and 200 mg to provide dosing flexibility with minimal patient inconvenience.

- No further formulation work is planned during the transition phase beyond preliminary experiments of limited scope. If a Go decision is made at the end of Phase I, a minimum of 9 months (3-4 months for bulk drug delivery and 6-8 months for PARD) will be needed to support Phase II studies. These activities will depend on the PK and safety results seen in the Phase I study and may be accelerated at risk based on preliminary results.

3.3. Toxicology Program

The toxicology program has been designed to provide the data required to support the Phase I clinical program. The Toxicology plan includes the following studies:

- Acute studies in rodents
- 1-month repeat dose studies in rats and monkeys
- Genotoxicity evaluation for mutagenic and clastogenic potential

One-month toxicology studies were started 6/00 with results available 9/00 to support the first-in-man multiple-dose study. On the basis of these studies several key safety determinations will be made: 1) identification of target organ toxicities, 2) determination of reversibility of tissue changes with drug discontinuation, 3) characterization of the contribution metabolites have on toxicity, and 4) recommendation for acceptable starting dose for human studies.

Challenges include: 1) measurement of five primary metabolites in plasma (and possibly tissues) as well as evaluation of their genotoxicity potential in a selection of mutagenicity and clastogenicity assays, and 2) decrease in plasma drug concentrations with repeated dosing may be a limiting factor for attaining target organ toxicity. Although autoinduction of ABT-518 metabolism is a likely cause, other possibilities exist, including formulation limitations and changes in absorption. These issues will be further characterized in the one-month studies.

3.4. Metabolism Program

Metabolism studies will continue throughout the transition period. Specifically, ongoing studies will focus on confirming the structure of circulating metabolites identified by co-chromatography and other, as yet unidentified, circulating plasma and tissue metabolites that were present in the 1-month non-GLP toxicology studies. Pending the successful synthesis of radiolabeled ABT-518, a mass balance and excretion study will be conducted to confirm quantitative recovery of dosed radioactivity and to determine the ultimate elimination products of ABT-518 *in vivo*. Basic *in vitro* studies will also be undertaken with ABT-518 and available metabolite standards to explain the metabolic disposition of ABT-518 in toxicological models (rat and/or monkey). Similar *in vitro* experiments in human models will be conducted in an attempt to describe likely metabolic disposition of ABT-518 and its metabolites in humans. These studies will be available prior to the initiation of the Phase I multiple-dose study.

3.5 Regulatory

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The Phase I multiple-dose study will be conducted ex-US without an IND. The Phase II program is planned to be conducted under a US IND. To facilitate initiation of the Phase II program, a small (14 patients) Phase I study will be submitted to the FDA to open the US IND. The IND will be opened 2Q01, prior to completion of the multiple-dose study and will facilitate the Phase II program by early identification of issues/requirements raised by the FDA. Opening the IND in 2001 could potentially reduce the development gap between Phase I and Phase II.

An additional benefit of this approach would be to establish a good working relationship with the FDA Oncology Division.

3.6. Phase I Multiple-Dose Study in Cancer Patients

The goals of the multiple-dose study in cancer patients are to determine the maximum tolerated dose (MTD), and evaluate the safety and pharmacokinetics of escalating doses of ABT-518. In the study 6-10 cohorts of cancer patients will be treated with a course of ABT-518, with a course being defined as 28 days of treatment. Each cohort will consist of a minimum of 3 patients diagnosed with refractory cancer. The starting dose for the 1st cohort will be determined by results of the one-month rat and monkey toxicity studies. Subsequent cohorts will be escalated by 25% - 100% dependent on the PK profile (parent and metabolites) and observed toxicity. Escalation will discontinue once dose-limiting toxicity occurs in 2/3 of patients in a cohort. This dose will become the MTD. An additional 6 patients will be exposed to ABT-518 at the previous dose level to acquire additional safety data.

Patients who wish to continue treatment with ABT-518 will be enrolled into an extension study, where they will be treated until dose limiting toxicities are reported or disease progression occurs.

3.6.1. Primary Objectives of the Study:

- Identification of an MTD.
- Assessment of the pharmacokinetics of the parent compound and achievement of a trough plasma concentration of 0.1 µg/ml.
- Assess clinical dosing frequency of QD and BID.
- Assess the safety profile after multiple doses in cancer patients with particular attention to joint toxicity.
- Recommend a Phase II dose(s).

3.6.2. Secondary Objectives:

- Evaluate the relationship of MTD to biologically significant inhibition.
- Assess a biomarker of activity in relation to drug exposure.
- Evaluate the metabolite profile in patients.

3.6.3. Decisions Based on Multiple-Dose Study Results

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At the completion of the Phase I multiple-dose study a Go/No Go decision will be made based on the safety and pharmacokinetic data. If targeted trough concentrations (0.1 µg/ml) after oral dosing with ABT-518 cannot be achieved, or if either an excessive dose (greater than 2 grams) or dosing frequency of more than BID is required, a recommendation on program discontinuation will be made. If results reveal considerable toxicity during the chronic administration of the targeted therapeutic dose, continued development of ABT-518 will be considered on the basis of potential benefit/risk ratio and the status of competition at that time. Evidence of joint toxicity reported during the study will be evaluated against what is known about the competitors' MMPIs.

4. Backup Strategy

From an intellectual property perspective, the MMP inhibitors field is quite mature. Over the past 10 to 15 years a steady stream of patent applications covering a range of structural classes have been published. Novel compositions of matter, particularly within the succinyl and biaryl hydroxamate classes, are now scarce. The biaryl ether retrohydroxamate class of MMP inhibitors provides Abbott with a patent niche within this very crowded field. The attributes and liabilities of this class have been fully explored by the Project Team; more than 390 retrohydroxamates were synthesized and extensively characterized over a 2-year period. While exceptions are always possible, it seems unlikely that the properties of ABT-518 can be vastly improved upon through further SAR within this series. Backup compounds to ABT-518 could be readily identified, yet they are apt to possess very similar properties. The opportunity to pursue other lead structures, generated through NMR screening or by other means, remains as a viable option, yet these endeavors must be viewed relative to other activities within Cancer Research. At this time the Project Team is applying no further effort to the discovery of novel MMP inhibitors.

5. Post Transition

The objective of the transition process is to conduct only those activities that are necessary to reach a Go/No Go decision for full development, thus minimizing the cost of early development. As such, once a Go decision is made following the Phase I program, there will be a delay of 6-8 months before initiating Phase II. This would be the time required to complete the necessary bulk drug synthesis, formulation activities, and regulatory preparation in order to proceed with the Phase II program. This gap could be minimized by resuming critical activities in support of Phase II prior to completion of the Phase I studies.

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6. Timeline/Milestones

	<u>Initiation</u>	<u>Completion</u>
• Bulk Drug Delivery (1.7 kg non-GMP)	Mar 00	Jun 00
• Toxicology	Jun 00	Oct 00
- One-month rat	Jun 00	Sep 00
- One-month monkey	Jun 00	Sep 00
- Genotoxicity & acute studies	Jun 00	Aug 00
• Go/No Go Decision Preclinical Safety	Sep 00	Sep 00
• Bulk Drug Delivery (3.8 kg GMP)	May 00	Jun 00
• Formulation Development & Clinical Supplies	Jun 00	Sep 01
• Phase I MD (28 days)	Nov 00	Dec 01
• Pre-IND Meeting with FDA	Feb 01	Feb 01
• Submit US IND	Apr/01	Apr/01
• Initiate US Phase I	Jun 01	Jun 01
• Bulk Drug delivery (10.0 kg GMP)	Jun 01	Aug 01
• Go/No Go Phase II	Dec 01	Dec 01
• Initiate Phase II	Apr 02	Apr 02

7. Transition Costs (\$MM)

	<u>2000</u>	<u>2001</u>
Clinical Program *	1.8	2.2
CMC (PARD, Chemical Sciences, Discovery)	2.3	2.3
Drug Safety	1.8	2.0
Other support costs [†]	0.1	0.2
Total	6.0	6.7

* Clinical Program = Grants, Data Mgt/STATS, Venture Management

[†] Other Support Costs = Regulatory Affairs, RQA, Medical Services

ABT-518 Transition Strategy
August 2000

Deposition Exhibit No. 6

P's Exhibit I

February 2001

ABT-518

Feb-01

ABT-518 (Matrix Metalloproteinase Inhibitor)

Franchise	Dev. Status	Brand Name	Generic Name	Patent Exp.	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100	2101	2102	2103	2104	2105	2106	2107	2108	2109	2110	2111	2112	2113	2114	2115	2116	2117	2118	2119	2120	2121	2122	2123	2124	2125	2126	2127	2128	2129	2130	2131	2132	2133	2134	2135	2136	2137	2138	2139	2140	2141	2142	2143	2144	2145	2146	2147	2148	2149	2150	2151	2152	2153	2154	2155	2156	2157	2158	2159	2160	2161	2162	2163	2164	2165	2166	2167	2168	2169	2170	2171	2172	2173	2174	2175	2176	2177	2178	2179	2180	2181	2182	2183	2184	2185	2186	2187	2188	2189	2190	2191	2192	2193	2194	2195	2196	2197	2198	2199	2200	2201	2202	2203	2204	2205	2206	2207	2208	2209	2210	2211	2212	2213	2214	2215	2216	2217	2218	2219	2220	2221	2222	2223	2224	2225	2226	2227	2228	2229	2230	2231	2232	2233	2234	2235	2236	2237	2238	2239	2240	2241	2242	2243	2244	2245	2246	2247	2248	2249	2250	2251	2252	2253	2254	2255	2256	2257	2258	2259	2260	2261	2262	2263	2264	2265	2266	2267	2268	2269	2270	2271	2272	2273	2274	2275	2276	2277	2278	2279	2280	2281	2282	2283	2284	2285	2286	2287	2288	2289	2290	2291	2292	2293	2294	2295	2296	2297	2298	2299	2300	2301	2302	2303	2304	2305	2306	2307	2308	2309	2310	2311	2312	2313	2314	2315	2316	2317	2318	2319	2320	2321	2322	2323	2324	2325	2326	2327	2328	2329	2330	2331	2332	2333	2334	2335	2336	2337	2338	2339	2340	2341	2342	2343	2344	2345	2346	2347	2348	2349	2350	2351	2352	2353	2354	2355	2356	2357	2358	2359	2360	2361	2362	2363	2364	2365	2366	2367	2368	2369	2370	2371	2372	2373	2374	2375	2376	2377	2378	2379	2380	2381	2382	2383	2384	2385	2386	2387	2388	2389	2390	2391	2392	2393	2394	2395	2396	2397	2398	2399	2400	2401	2402	2403	2404	2405	2406	2407	2408	2409	2410	2411	2412	2413	2414	2415	2416	2417	2418	2419	2420	2421	2422	2423	2424	2425	2426	2427	2428	2429	2430	2431	2432	2433	2434	2435	2436	2437	2438	2439	2440	2441	2442	2443	2444	2445	2446	2447	2448	2449	2450	2451	2452	2453	2454	2455	2456	2457	2458	2459	2460	2461	2462	2463	2464	2465	2466	2467	2468	2469	2470	2471	2472	2473	2474	2475	2476	2477	2478	2479	2480	2481	2482	2483	2484	2485	2486	2487	2488	2489	2490	2491	2492	2493	2494	2495	2496	2497	2498	2499	2500	2501	2502	2503	2504	2505	2506	2507	2508	2509	2510	2511	2512	2513	2514	2515	2516	2517	2518	2519	2520	2521	2522	2523	2524	2525	2526	2527	2528	2529	2530	2531	2532	2533	2534	2535	2536	2537	2538	2539	2540	2541	2542	2543	2544	2545	2546	2547	2548	2549	2550	2551	2552	2553	2554	2555	2556	2557	2558	2559	2560	2561	2562	2563	2564	2565	2566	2567	2568	2569	2570	2571	2572	2573	2574	2575	2576	2577	2578	2579	2580	2581	2582	2583	2584	2585	2586	2587	2588	2589	2590	2591	2592	2593	2594	2595	2596	2597	2598	2599	2600	2601	2602	2603	2604	2605	2606	2607	2608	2609	2610	2611	2612	2613	2614	2615	2616	2617	2618	2619	2620	2621	2622	2623	2624	2625	2626	2627	2628	2629	2630	2631	2632	2633	2634	2635	2636	2637	2638	2639	2640	2641	2642	2643	2644	2645	2646	2647	2648	2649	2650	2651	2652	2653	2654	2655	2656	2657	2658	2659	2660	2661	2662	2663	2664	2665	2666	2667	2668	2669	2670	2671	2672	2673	2674	2675	2676	2677	2678	2679	2680	2681	2682	2683	2684	2685	2686	2687	2688	2689	2690	2691	2692	2693	2694	2695	2696	2697	2698	2699	2700	2701	2702	2703	2704	2705	2706	2707	2708	2709	2710	2711	2712	2713	2714	2715	2716	2717	2718	2719	2720	2721	2722	2723	2724	2725	2726	2727	2728	2729	2730	2731	2732	2733	2734	2735	2736	2737	2738	2739	2740	2741	2742	2743	2744	2745	2746	2747	2748	2749	2750	2751	2752	2753	2754	2755	2756	2757	2758	2759	2760	2761	2762	2763	2764	2765	2766	2767	2768	2769	2770	2771	2772	2773	2774	2775	2776	2777	2778	2779	2780	2781	2782	2783	2784	2785	2786	2787	2788	2789	2790	2791	2792	2793	2794	2795	2796	2797	2798	2799	2800	2801	2802	2803	2804	2805	2806	2807	2808	2809	2810	2811	2812	2813	2814	2815	2816	2817	2818	2819	2820	2821	2822	2823	2824	2825	2826	2827	2828	2829	2830	2831	2832	2833	2834	2835	2836	2837	2838	2839	2840	2841	2842	2843	2844	2845	2846	2847	2848	2849	2850	2851	2852	2853	2854	2855	2856	2857	2858	2859	2860	2861	2862	2863	2864	2865	2866	2867	2868	2869	2870	2871	2872	2873	2874	2875	2876	2877	2878	2879	2880	2881	2882	2883	2884	2885	2886	2887	2888	2889	2890	2891	2892	2893	2894	2895	2896	2897	2898	2899	2900	2901	2902	2903	2904	2905	2906	2907	2908	2909	2910	2911	2912	2913	2914	2915	2916	2917	2918	2919	2920	2921	2922	2923	2924	2925	2926	2927	2928	2929	2930	2931	2932	2933	2934	2935	2936	2937	2938	2939	2940	2941	2942	2943	2944	2945	2946	2947	2948	2949	2950	2951	2952	2953	2954	2955	2956	2957	2958	2959	2960	2961	2962	2963	2964	2965	2966	2967	2968	2969	2970	2971	2972	2973	2974	2975	2976	2977	2978	2979	2980	2981	2982	2983	2984	2985	2986	2987	2988	2989	2990	2991	2992	2993	2994	2995	2996	2997	2998	2999	3000
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ABT-518 is a metalloproteinase inhibitor that selectively targets MMP-2 and MMP-9, metalloproteinases that have been implicated in the progression of cancer in preclinical studies. ABT-518 inhibits tumor growth in a variety of murine tumor models when administered alone, or in combination with cytotoxic agents. ABT-518 also blocks blood vessel formation in a murine angiogenesis model.

Description

Unit	Value	CAGR	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	2100	2101	2102	2103	2104	2105	2106	2107	2108	2109	2110	2111	2112	2113	2114	2115	2116	2117	2118	2119	2120	2121	2122	2123	2124	2125	2126	2127	2128	2129	2130	2131	2132	2133	2134	2135	2136	2137	2138	2139	2140	2141	2142	2143	2144	2145	2146	2147	2148	2149	2150	2151	2152	2153	2154	2155	2156	2157	2158	2159	2160	2161	2162	2163	2164	2165	2166	2167	2168	2169	2170	2171	2172	2173	2174	2175	2176	2177	2178	2179	2180	2181	2182	2183	2184	2185	2186	2187	2188	2189	2190	2191	2192	2193	2194	2195	2196	2197	2198	2199	2200	2201	2202	2203	2204	2205	2206	2207	2208	2209	2210	2211	2212	2213	2214	2215	2216	2217	2218	2219	2220	2221	2222	2223	2224	2225	2226	2227	2228	2229	2230	2231	2232	2233	2234	2235	2236	2237	2238	2239	2240	2241	2242	2243	2244	2245	2246	2247	2248	2249	2250	2251	2252	2253	2254	2255	2256	2257	2258	2259	2260	2261	2262	2263	2264	2265	2266	2267	2268	2269	2270	2271	2272	2273	2274	2275	2276	2277	2278	2279	2280	2281	2282	2283	2284	2285	2286	2287	2288	2289	2290	2291	2292	2293	2294	2295	2296	2297	2298	2299	2300	2301	2302	2303	2304	2305	2306	2307	2308	2309	2310	2311	2312	2313	2314	2315	2316	2317	2318	2319	2320	2321	2322	2323	2324	2325	2326	2327	2328	2329	2330	2331	2332	2333	2334	2335	2336	2337	2338	2339	2340	2341	2342	2343	2344	2345	2346	2347	2348	2349	2350	2351	2352	2353	2354	2355	2356	2357	2358	2359	2360	2361	2362	2363	2364	2365	2366	2367	2368	2369	2370
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February 2001**ABT-518****Monthly Highlights - Key Project Progress**

- Study initiation visits were conducted on 2/14 and 2/15.

Next Quarter's Key Project Progress

Target Date

3/12

3/31

6/1

6/30

Key Progress Markers

- First patient enrolled
- Preliminary results from 6-week rat hepatotoxicity study
- Pre-IND meeting with FDA
- Preliminary results from 3-month rat chronic toxicity study

Key Project Issues and Risks				Resolution Date
Risk or Issue	Potential or Known Impact	Checklist that applies and Describe Impact	Strategy / Progress	Planned / Actual
Identification of FDA requirements for cytostatic agents in oncology drug development.	<input type="checkbox"/> Cost <input type="checkbox"/> Time <input type="checkbox"/> Profile <input checked="" type="checkbox"/> Regulatory	Phase I IND study to Transition program to solicit FDA input.	Clinical	6/1/01
Key tox finding was hepatotoxicity in one-month rat study. <i>In-vitro</i> and <i>in-vivo</i> data indicate a potential for mechanism based drug interactions.	<input type="checkbox"/> Cost <input type="checkbox"/> Time <input checked="" type="checkbox"/> Profile <input checked="" type="checkbox"/> Regulatory	The Phase I first-in-man protocol has been designed to address these issues. A 6-week tox and metabolism studies have been completed. Results are under review. A 3-month rat toxicity study is ongoing.	Toxicology/ Metabolism	7/1/01

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February 2001

ABT-518

Key Project Status and Risks		Resolution Date	
Risk or Issue	Potential Known Impact Check all that apply and describe impact	Strategy / Progress	Area of Responsibility
As several competitors are in Phase II/III, ABT-518 product profile will need to demonstrate advantage over the other compounds (i.e., safety/efficacy)	<input type="checkbox"/> Cost <input type="checkbox"/> Time <input checked="" type="checkbox"/> Profile <input type="checkbox"/> Regulatory	Ongoing analysis and comparison of competition throughout transition. ABT-518 has the potential to be the best in class compound. Pfizer (Agouron) announced 8/4/00 that they were stopping Phase III trials of pinomastat in advanced prostate and NSCLC because "primary efficacy objectives were not met". They are continuing trials in less advanced tumors, e.g., glioma and NSCLC, and will start trials in two additional tumor types. Efficacy was shown with marimastat in less advanced gastric cancer, but British Biotech announced on 9/27/00 that marimastat in combination with carboplatin was no better than carboplatin alone in advanced ovarian cancer. Marimastat development was discontinued on 2/15/01. Both the Pfizer compound and British Biotech's compound are hindered by dose-limiting joint toxicity.	Competitive Environment
	<input type="checkbox"/> Cost <input type="checkbox"/> Time <input type="checkbox"/> Profile <input type="checkbox"/> Regulatory		

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February 2001**ABT-518****Key Activities**

Activity	Commercial	LBE	Actual
Market research to assess commercial potential of cancer types, both US and Ex-US		4/2001	
Assessment of patient compliance (for revision of forecast)		3/2001	
Assessment of off-label vs. spillover use (for revision of forecast)		3/2001	
Assessment of cancer market growth (for revision of forecast)		4/2001	
Assist with advisory planning		4/2001	
Development of brand and generic names		Late 2001	

Activity	Plan	Actual
Phase I Formulation	10/2000	
Phase II Formulation		
Formulation for Bio Study		
Phase III Clinical Supplies Manufactured		
NDA Lots (3) Completed		
Completion of 1 Year Stability for NDA		
Formulation Peer Review		

Drug Substance**Plan Date: 3/2000**

Activity	KG	Plan	Actual	Actual Projected Cost/kg
Chem Scien (GLP)	3.0/1.7	6/2000	6/16/00	\$133,300
Chem Scien (GMP)	2.0/3.8	6/2000	6/29/00	\$133,300
Chem Scien	15.0	6/2001		
SPD				
SPD				
SPD				
Demo Lot				
NDA Lot #1				
NDA Lot #2				
NDA Lot #3				
Validation Lot				

Toxicology**Plan Date: 3/2000**

Toxicology Activity	Planned Start	Actual Start Date	Report Completed
Gene Toxicology	5/2000		
Acute Studies	5/2000		
2-Week Monkey (non-GLP)	12/1999	12/14/99	
1-Month Rat (non-GLP screening)	12/1999	12/14/99	
1 Month Rat (GLP)	6/2000	6/27/00	
1 Month Monkey (GLP)	6/2000	6/28/00	
3 Month Rat	1/2001	1/2/01	
3 Month Mouse MTD			
SEG I and SEG II			
SEG III Rat (post natal development)			
6 Month Rat			
1 Year Monkey			
Carcinogenicity (2 yr) Rat			
Carcinogenicity (2 yr) Mouse			

4 of 4

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February 2001**ABT-518****All Clinical Studies:**

Protocol Number	Phase	Study Name	Protocol Number	Phase	Study Name	Start 1 st Pt. Dosed	End (Last CRF In)	Patients	
								Target	Current
M00-235	I	MD Study in cancer patients				228		40	
TBD	I	IND Study						20	

5 of 5

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February 2001**ABT-518****Ongoing Clinical Studies** (List first time in man, Phase II Dose-Ranging and Pivotal Trials)

MXX-XXX - TITLE

M00-235 - Phase I MD in cancer patients

Protocol:

Objective:

Determine MTD and safety profile in cancer patients

ABT-518 Doses:

25, 50, 100, 200, 400, 800, 1200, 1600, 2000 mg/day

Comparator Doses:

N/A

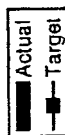
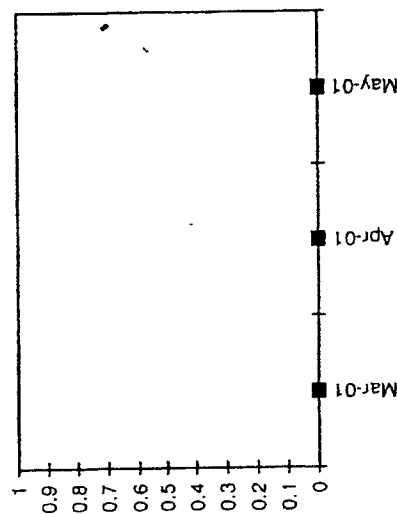
Target Enrollment:

40

Status:

Study initiated, clinical supplies delivered

Major Findings:

**Enrollment**(Author:
Double click on chart to
edit)

D477Z:\MPSRs\ABT-518.doc

6 of 6

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Deposition Exhibit No. 9

P's Exhibit M

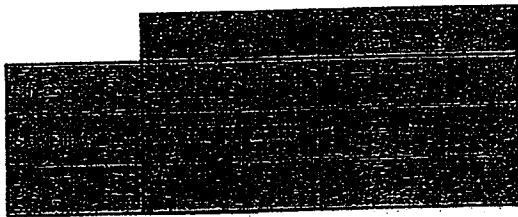
Abbott Portfolio Review

March 7-9, 2001

- Project ABT-518
- Compound Matrix Metalloproteinase Inhibitor
- Presenter Perry Nisen
- Project Team Members
A. Nabulsi (VH), T. Janus (MD), D. D'Amico (CPM)

ABT-518

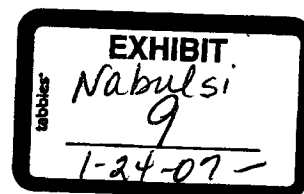
- ◆ Target indication: Solid tumors.
- ◆ Targeted unmet medical need: Cancer
- ◆ Target product profile vs. current gold standard:



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ABBT 0013224



ABT-518

◆ Key pre-clinical findings:

- Pharmacology
 - Potent and highly selective (gel-A and gel-B) MMP inhibitor
 - Anti-tumor activity seen in numerous murine cancer models
 - Inhibition of tumor growth is dose dependent
 - Blocks vessel formation in a mouse model of angiogenesis
- Pharmacokinetics / Metabolism in animals
 - Sustained plasma concentrations following single-dose in monkeys
 - Oral bioavailability between 68 and 93% in animals
 - Multiple metabolites are produced after repeat dosing in rats and dogs
- Toxicology
 - No meaningful effects in genotoxicity, cytotoxicity or ligand binding assays
 - No remarkable cardiovascular effects in dogs
 - Steatosis seen in high-dose rats two weeks after drug stopped

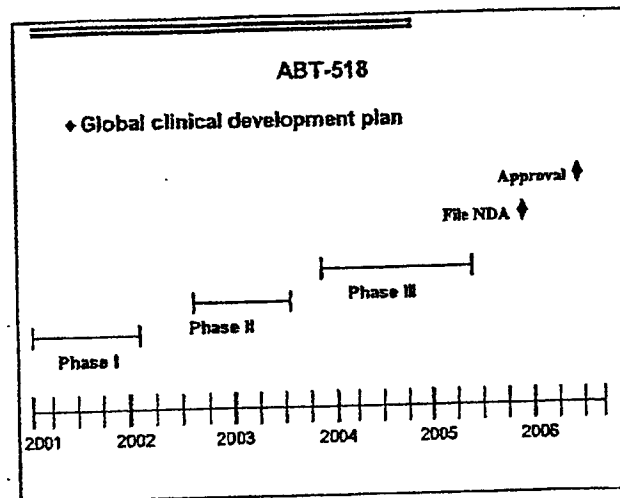
ABT-518

◆ Chemistry and Manufacturing

- Drug substance
 - Six steps from commercial starting materials
 - 3-month turnaround time to manufacture
 - Manufactured at Abbott
- Drug product
 - Neat drug in a capsule (25 and 200 mg) for Phase I
 - Hand-fill or semi-automation at a third party manufacturing facility (Phase I)
 - Formulation development work will begin post Phase II Go/No Go decision

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ABBT 0013225



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ABT 0013226

ABT-518

♦ **Clinical development budget**

Phase	Funding (\$MM)
Pre-Clinical	5
Phase I	12
Phase II	47
Phase III	76

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ABBT 0013227

ABT-518

◆ Phase I study:

Multiple-dose study in patients with advanced cancer

- Objectives
 - Establish safety profile
 - Determine the maximum tolerated dose (MTD)
 - Assess PK
 - Determine Phase II dose
- Design
 - 28 days + extension
 - Single-dose of drug administered on Day 1; resume dosing (daily) on Day 4
 - Approximately 40 patients; 3 patients per dose
 - Add 6 or more patients at MTD to collect additional safety information
 - Doses: 25, 50, 100, 200, 400, 800, 1200, 1600, 2000 mg/day

ABT-518

◆ Phase I plan:

IND Study

- Objectives
 - PD-guided Phase II dose selection
 - Long-term safety
- Design
 - Multiple dose escalation study
 - Assess MMP activity in accessible tumors
 - Melanoma
 - Head and Neck Cancer
 - Approximately 20 patients

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ABBT 0013228

ABT-518

♦ Phase II development plans:

- 3 Studies
 - 3 Tumor types as defined by Phase I and animal efficacy
 - 150 patients per study
- Dose finding
- Assess safety issues identified in Phase I
- Thirteen month duration

ABT-518

♦ Phase III plan:

- Demonstrate improvement in survival or TTP in combination with cytotoxic therapies

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ABBT 0013229

Strategic Summary
<p align="center">ABT-518</p> <p>♦ Key project strengths / positives:</p> <ul style="list-style-type: none"> - Product attributes <ul style="list-style-type: none"> • Highly selective for the inhibition of galeinases A & B • Very potent • No joint-toxicity expected • Potentially best in class - Technology / Innovation <ul style="list-style-type: none"> • Oral, once-a-day dosing - Time to market <ul style="list-style-type: none"> • Potential for fast-track approval • Launch 2008 - Business franchise strength <ul style="list-style-type: none"> • Comprehensive oncology franchise • Synergies with HPD and ADD - Other relevant points <ul style="list-style-type: none"> • Competitors in class • Non-oncologic indications <ul style="list-style-type: none"> • Multiple schedules • Preliminary safety • Arthritis

Strategic Summary
<p align="center">ABT-518</p> <p>♦ Potential issues / Threats / Negatives:</p> <ul style="list-style-type: none"> - Toxicity / side effects <ul style="list-style-type: none"> • Metabolites that may accumulate over time • Potential mechanism-based drug interaction (CYP3A inducer-inhibitor) • Microvascular and macrovascular stenosis in rat study - Manufacturing / cost of goods - No issues anticipated - Efficacy <ul style="list-style-type: none"> • Data released from competitors may cast doubt on class - Clinical recruitment problems <ul style="list-style-type: none"> • Extensive protocol prohibited medications list - Regulatory risk <ul style="list-style-type: none"> • No precedent for cytostatic drug approval • Undefined clinical endpoints • Competitor data may pose additional development hurdles - Technical risks - No issues anticipated - Other relevant issue <ul style="list-style-type: none"> • No good models for selection of dose, regimen and responsive tumor types • PD marker selection

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ABBT 0013230

ABT-518		Strategic Summary
<p>◆ Key decisions:</p> <ul style="list-style-type: none"> - Important upcoming decisions <ul style="list-style-type: none"> • Transition team Go/No Go Phase II - 12/01 - Proposed budget (2001, and all years to launch) 		
Year	R&D per year (\$MM)	
2001	7	
2002	38	
2003	56	
2004	29	
2005	23	
2006	8	

ABT-518		Strategic Summary
<p>◆ Key decisions:</p> <ul style="list-style-type: none"> - Evaluate safety at multiple doses and dose regimens - Dose and regimen selection for Phase II - Tumor type selection for Phase II - Clinical trial design to demonstrate efficacy 		

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ABBT 0013231

ABT-518		Strategic Summary
• Proposed action plans		
- Manufacturing		
• Initiate formulation work post Phase II Go/No Go		
- Nonclinical		
• Additional toxicology and metabolism studies are underway to explore the CYP3A and sterol issues		
- Clinical		
• Measure metabolites in Phase I		
• Assess bioactivity via PD markers in Phase I		
• Hold a Pre-IND meeting with the FDA to discuss endpoints		
- Contingency plan		
• Pursue alternative indications		
- Multiple scenarios		
- Prohibitive safety/toxicity		
- Attrition		

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ABBT 0013232

Deposition Exhibit No. 10

P's Exhibit N

MMPI MONTHLY MEETING AGENDA

3/8/2001, 10:30-12:00, AP6A-1A

Objectives: To Review MMPI Project Status

- B.H. Pre-IND Timeline
- TJ PK Validation
- * Ask if PD data will ever be submitted

NOTES If so, audit.

b7c Ami.
No**I. Clinical - A. Nabulsi/ D. D'Amico**

JERHEADS

- Leiden portfolio review 3/7
- M00-235 sites initiated 2/14 & 2/15
- Drug shipped 2/28 & 3/1
- First patient: Monday (3/12)
- IND timeline being revised (Mtg 3/9)

①

How can we continue if competition is dropping out? Pre-clinically we differ. Comp to low doses, mono vs combo, skipped PH II, not right stage tumors
 → We'll look @ ASCO & AACR for comp info
 → We'll know in 3-6 mo where we'll stand
 Todd Leaver for AACR by Apr 22nd - He'll look @ abstracts upon

II. Toxicology - K. Loberg

JERHEADS

- 6 week rat study completed
- 3 month rat - 1st necropsy 4/10/01

→ VANDERBILT TELECONFERENCE ON 3/12 TO DISCUSS THE IND STUDY

* FIND OUT CANCER TYPE FOR 1ST PATIENT**III. PK - B. Carr/ M. Rieser/ Tawakol**

JERHEADS

- PK method validation in human plasma is complete for all 7 analytes.
- Finishing re-analysis of metabolites from toxicology studies (last fall).

②

3 months: In high dose group
 ↓ body weight gain, dehydration, alopecia; similar results to previous study on 070
 6 wk: In life dose, necropsy all, assembling data on mitochondrial assays; High dose group did recover body weight and food consumption after off drug
 • Is there a CNS involvement? Bill Bracken is concerned w/ ↓ body weight; possibly not just 2nd & 3rd .

Take in vitro data plus data on 070
 by next mth

IV. PARD - J. Cannon/ T. Garavalia

JERHEADS

- Capsule update: Feton run at MDS Pharma) completed; 200mg capsules 73% yield

③

Call site w/ Matt & Tawakol to discuss status their validation

V. CAPD - S. Wittenberg

- No Update

Needed for IND. When will be available? Bill Bracken on try of it.

VI. Discovery - S. Davidson

- No Update

VII. Metabolism - D. Hickman

- No Update

VIII. Next Team Venture Meeting

When: Thursday, April 12, 2001

Where: AP6A-1A

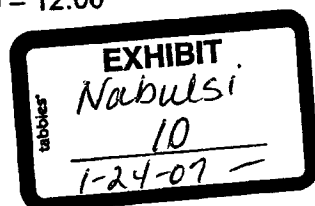
Time: 10:30 - 12:00

④ - Standard Deviation of empty capsule > than expected
 - Dog behaved differently when filling the capsules

- Zoo rejects → Use for enrichment work. Must be designated "experimental". Next time - will incorporate rework steps for GMP use.

- June run @ MDS 2nd IDG facility booked

- ALERT Gene stability update, pitting, drugs in bottle - No - ...



Deposition Exhibit No. 11

P's Exhibit O

MMPI WORKING GROUP MEETING MINUTES

3/8/01

Objective: Overall Project UpdateClinical Update*Azmi Nabulsi & Diane**D'Amico*

- A brief summary of the Leiden Portfolio Review held 3/7/01 – 3/9/01 was presented. Questions were raised regarding ABT-518 since several competitor MMPi's have been discontinued. We will proceed with the phase I trial. Pre-clinically our compound differs from the competition. In addition, the competitors may have dosed too low, may not have selected the proper tumor stages, and skipped Phase II development.
- The two M00-235 sites were initiated in February. Drug was shipped to both sites and the first patient is expected 3/12/01.

Toxicology Review*Lise**Loberg*

- An update of the two current toxicology studies was presented (see attached slides – Tox 030801A.xls and Tox 030801B.doc)
- Preliminary results from the three-month oral toxicity study in rats were discussed. Changes were seen in the high dose group (300 mg/kg) including decreased body weight, decreased food intake, dehydration and alopecia.
- The first three-month necropsy is planned for 4/10/01.
- The in-life phase of the six-week study has been completed. The process of integrating the mitochondrial function results with clinical pathology and histopathology has been initiated.

PK*Tawakol El-Shourbagy*

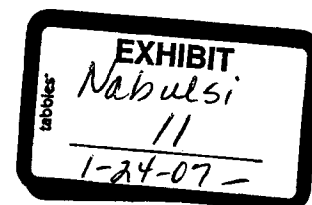
- The PK method validation process at Abbott is complete. NKI has not completed their PK method validation process to date. A teleconference will be scheduled within the next few days to determine the status of the PK method validation process at NKI.
- With the PK method validation complete, internal efforts will be directed towards finishing re-analysis of metabolites from toxicology studies conducted last fall; this work is needed for the IND.

PARD*John Cannon*

- An update of clinical supplies was presented (see attached slides – PARD 030801.doc).
- The first 200mg capsule campaign was completed by MDS Pharma Services in Tampa FL. A lower than expected yield rate of 73% resulted in the production of 4,870 acceptable capsules, of which 4,140 capsules will be sent for clinical supply. The low yield rate may be due in part to the larger than expected standard deviation variation for the empty capsules and to the process itself. PARD is looking into the exact cause(s).
- The rejected capsules and recovered bulk drug (deemed experimental) will be used for formulation and process development work. A rework step can be added to future runs to improve yield.

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ABBT300143



MMPI WORKING GROUP MEETING MINUTES

3/8/01

- The next 200mg capsule campaign is planned for June (10,000 capsules, 2 kg bulk drug). Based on the Phase I study in the Netherlands and the IND study design, the possibility of alternate capsule size (i.e., 50 or 100mg) has been discussed. PARD needs a 12-week lead-time from the time of dosing if the capsule size changes from the originally planned 200mg.
- The six-month stability data on 25mg capsules stored in bottles at 40C/75% RH showed some pitting (etiology unknown). At this time, there were no concerns with capsules stored at room temperature.

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ABBT300144

Deposition Exhibit No. 12

P's Exhibit PJ

Jim,

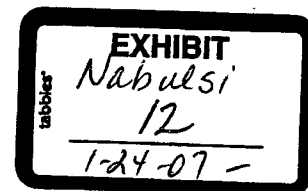
Greetings.

We had a project review with upper management this Wednesday. During this review there was a concern regarding the continuation with ABT-518 development. Although, we thought that we will be allowed to continue at this time, I and Perry have learned, 45 minutes ago, that we should stop all development activities immediately. As much as I hate to do this to you, I would like to ask you to communicate with Drs. Zonnenberg and Schellen that we are not proceeding with the trial as a result of the projects re-prioritization following the acquisition of Knoll. I will call you on your mobile phone (I do not have your home #) to discuss this further with you and check your comfort level with this very difficult task. If you prefer to call me, my home number: 847-382-3818, mobile : 847-380-5830. As you know, at AZU they are expecting a patient Monday morning, so this has to be done ASAP.

I did not have the chance to tell Todd and Diane D. this news since I was informed late in the day and they have left already. So please do not copy others until I have a chance to inform them directly.

Thanks

Azmi



Deposition Exhibit No. 13

P's Exhibit BL

Timeline of events occurring with Study M00-235 in the Netherlands
--

14 february 2001	Site initiation Schellens, Amsterdam
15 february 2001	Site initiation Zonnenberg, Utrecht
7 march 2001	Nisen (DVP, Oncology, Abbott US) and Nabulsi (Oncology head, Abbott US) attended Abbott senior management review: "concern regarding the continuation of ABT-518 development"
11 march 2001	Nabulsi (Oncology head, Abbott US) calls Looman (ass. Med Dir Oncology, Abbott NL) to inform about immediate stop ABT-518 project (and thus study M00-235). Janus (Med. Dir Oncology, Abbott US) and D'Amico (PM, Oncology, Abbott US)
12 march 2001	Looman calls Schellens and Zonnenberg and requests to NOT enroll any patients due to decision Abbott to stop study Zonnenberg has enrolled patient 1001; Schellens did not enrol a patient awaiting BoD approval D'Amico sends Beerepoot (sub-I, Utrecht) memo to allow continuation with pat 1001 and await further news (expected on 13 Mar 01); no new patients to be enrolled. Schellens also informed by memo (D'Amico).
13 march 2001	Abbott informs Schellens and Zonnenberg that study hold has been lifted.
23 march 2001	1001 stops study due to DP (and dies on 30 apr 01 due to cerebral mets)
26 march 2001	Schellens enrolls Pat 1002
23 april 2001	Zonnenberg enrolls pats 1003 & 1004
25 april 2001	Pat 1002: SAE (dyspnea/pleural effusion), probably not related
12-16 may 2001	ASCO: discussion by Abbott and sites: no safety issues: go to level 2 (50 mg)
18 may 2001	Memo Janus confirming escalation to level 2 (50 mg) per 21 May 2001
21 may 2001	Pat 1002 withdraws consent (due to SAE) Start patient first patient on 50 mg at NKI - 1101 JDE
22 may 2001	Start AE of 1004 (day 29 of study) - Rise of Creatinin: possibly related
25 may 2001	Hospitalization pat 1004: AE → SAE
25 may 2001	Initial SAE report pat 1004 to Abbott Safety Desk: relationship: possible related due to rising creatinin: DLT
26 may 2001	Stop medication pat 1004 to allow decrease of toxicity to within one level of baseline
30 may 2001	Follow-up SAE report; relationship: possible caused by kidney failure
30 may 2001	Zonnenberg sends letter to EC regarding pat 1002 reporting SAE: relapse pleural effusion needs to be changed into dyspnea
1 june 2001	MMP1 project (ABT-518) deemed a No/Go by senior management
5 june 2001	Teleconference Abbott - Zonnenberg: relationship SAE 1004 is still possibly related, but needs to be probably not related, if enrollment of new patients at level 2 (50 mg) can continue. Schellens; 2 nd patient 1102 NKI is waiting to be included. Decision Abbott to suspend enrollment to clarify renal toxicity, based on suggestion by Zonnenberg. Patient 1004 stops study due to SAE
12 june 2001	Verbal announcement of Abbott (Nabulsi) to stop study to Schellens and Zonnenberg
14 june 2001	Teleconference with Voest to officially inform him of study termination
19 june 2001	1003 stops study due to DP
21 june 2001	Teleconference with Schellens to officially inform him of study termination After this call, an official study termination letter was sent to Schellens and Zonnenberg
22 june 2001	Receipt of registration form of proposed 2 nd patient at 50 mg by Schellens
22 june 2001	Memo Janus: relationship SAE 1004 will be changed to: probably not; Schellens to announce 2 nd patient at 50 mg; official paperwork from Zonnenberg to confirm changed relationship pending



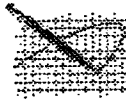
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25 June 2001	2nd patient at 50 mg included 1102 by Schellens, however no documentation of changed relationship received from Zonnenberg. Patient should have received 25 mg due to possible DLT
26 June 2001	Visit Nabulsi to both sites to explain termination of study
6 July 2001	Conference call with Schellens asking him to not enroll new patients at 50 mg; Statement from Schellens that no more patients as of 6 Jul 01 except for pat 1101 have been enrolled at 50 mg
7 July 2001	Memo Janus to indicate that relationship has not changed, so any new patient should receive 25mg.
11 July 2001	Memo of datanurse of Zonnenberg signaling unawareness of changed relationship from probably not back to possible
12 July 2001	Renewed request to Schellens to confirm that no new patients after pat 1101 have been enrolled; Additional information received by Janus about inclusion of second patient 1102 on 25 June 01
25 July 2001	Memo from Schellens to inform Abbott that patient 1102 will continue on 50 mg, no drug related toxicities.
27 July 2001	Memo Knight (PM, Abbott Oncology US): Nabulsi agrees with proposed strategy by Schellens. Protocol deviation noted and will be reported correctly.
31 July 2001	Zonnenberg letter to Janus: Relationship SAE pat 1004 remains possibly related; recommendation Zonnenberg to add 3 more patients @ 25 mg.
10 Dec 2001	Zonnenberg sends corrective letter to EC to change description of SAE pat 1002 from "relapse pleural effusion" to "dyspnea". Content and outcome SAE have not changed.
30 Nov 01	Close out visit Schellens
11 Dec 2001	Close out visit Zonnenberg

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ABBT0518378

Deposition Exhibit No. 14

P's Exhibit S



Diane L
D'Amico /LAKE/PPRD/ABBO
TT

03/12/2001 03:08 PM

To jhm@nki.nl

j.maaskant@telescan.nki.nl, ldvl@telescan.nki.nl, Jim
Looman/HOOFDDORP/A/ABBOTT@ABBOTT, Else
Meijer/HOOFDDORP/A/ABBOTT@ABBOTT, Willy
Jansen/HOOFDDORP/ADD/ABBOTT@ABBOTT, Todd J
Janus/LAKE/PPRD/ABBOTT@ABBOTT, Paige
Gjelsten/LAKE/PPRD/ABBOTT@ABBOTT, Lori V
Rountree/LAKE/PPRD/ABBOTT@ABBOTT, Azmi A
Nabulsi/LAKE/PPRD/ABBOTT@ABBOTT, Diane C
Bronson/LAKE/PPRD/ABBOTT@ABBOTT, Robert
Hansen/LAKE/PPRD/ABBOTT@ABBOTT

bcc

Subject M00-235 Update

Dear Professor Schellens,

As you know, we have been instructed to halt the M00-235 study. I assume that you know that the AZU enrolled a patient into the study today.

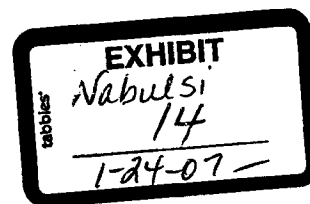
At this time, we have instructed the AZU to proceed with the M00-235 patient per the protocol until they hear from us otherwise. We hope to have further instructions by tomorrow (Tuesday, 13Mar01).

We ask that you refrain from enrolling any additional patients at your site at this time.

Thank you for your patience and understanding in this matter.

Best regards,

Diane



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ABBT0060788

Deposition Exhibit No. 17

P's Exhibit AP



Diane L
D'Amico /LAKE/PPRD/ABBO
TT
05/25/2001 03:52 PM

To Lise I Loberg/LAKE/PPRD/ABBOTT@ABBOTT
cc Diane C Bronson/LAKE/PPRD/ABBOTT@ABBOTT
bcc
Subject Re: ABT-518 Tox

Lise-

Maybe you read the email below wrong. Can we wait until Diane says Yes/No? I don't want you to start something that is still on hold.

Thanks,

Diane

Lise I Loberg



Lise I Loberg
05/25/01 03:23 PM

To: Diane L D'Amico/LAKE/PPRD/ABBOTT@ABBOTT
cc: Diane C Bronson/LAKE/PPRD/ABBOTT@ABBOTT
Subject: Re: ABT-518 Tox

Will do!
Diane L D'Amico



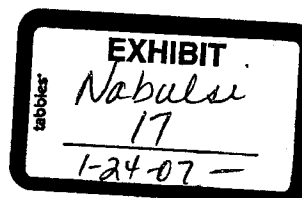
Diane L D'Amico
05/25/01 03:01 PM

To: Diane C Bronson/LAKE/PPRD/ABBOTT@ABBOTT
cc: Lise I Loberg/LAKE/PPRD/ABBOTT@ABBOTT
Subject: ABT-518 Tox

Diane,

Can Lise proceed with any of the ABT-518 activities that were previously put on hold (i.e., very long chain fatty acid sample analysis from the 6-week rat study and histopath from the 3-month rat study)?

Diane



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ABBT0061200

Deposition Exhibit No. 21

P's Exhibit MI

MMPI MONTHLY MEETING AGENDA

4/12/2001, 10:30-12:00, AP6A-1A

Objectives: To Review MMPI Project Status

Anne Hagey - Rolak-S
MD

NOTES

1. Toxicology - L. Loberg

- Results from 6 week rat study
- 3 month rat – (RX phase ends this week)

II. PK - B. Carr/ M. Rieser

- No update

III. PARD – J. Cannon/ T. Garavalia/ S. Wittenberger

- Capsules analysis, Feton run- 101% against claim
- Process research is making additional drug

IV. Discovery – S. Davidson

- **No Update**

Y. Metabolism – D. Hickman

- Rat ADME study update
 - ↳ Single Dose

VI. Clinical—D. D'Amico

- PK method validation update- Netherlands
- Day 1 PK samples from 2 patients collected
- 2 patients enrolled, 1 active
- 2 patients scheduled to enroll 4/23
- IND document collection continues

Next Team Venture Meeting

When: Thursday, May 10, 2001

Where: AP6A-1A

Time: 10:30 - 12:00

* Per Day: Kill scenario: Liden wants to make
Gophers Go Decision Based
on Computer Data @
ASCO; committee

Field Study: NH: Nov / Dec - in earliest start

I.

[illegible]

Will proceed
w/ process
R.S.

Wittenberger

to determine effects on protein synthesis & metabolism ULEFA

VLCFA very long Chain Fatty Acids
why? ↓ weight & food consumption -
HD animals only
↓ effects on activity
not an uncommon finding
One study does not warrant anything not
a explanation for steatosis alone

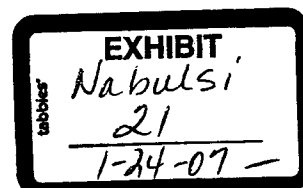
7/16 phenomenon of ketosis
 even so acute proinflammatory
 20 SEE proliferation? time test. Δ ? accumulation of antibodies
 stop drug. Start eating again.
 Give bundle it.

Next two: in life 3m. clinical observation.

III: Still investigation how yield
to bulk density of sieved drug
more it packs more you shake
— bulk density? (more compact) over time
and ② higher standard deviation of
empty capsules in more narrow
range for all capsules

Steps: Preparing to make more markets
3 steps / ~~month~~ ^{ready} in Jan/Feb
each run will take 2 wks
expant 15 kg
+ means to find out pilot plant
viability
Steps - Put on Hold now; Will get back to you
when we most likely
Diplo - look @. Remain costs (will be
same?)
W.H. Khan then need to be carried

II - Peak of elimination - rises almost steadily
- profile of metabolites very different in
 - like duct animals as feces
still - 1/2 life of 2 days for metabolites (picks up
 - very poor left off) - we got
 - take great note of PH



sulphonic acid → seen in rat tissue extracts now - wasn't seen before
 - presume it's sulphonic acid (metabolite that has long 1/2 life)
 - why didn't we see sulphonic acid?
 We didn't see it in monkeys, etc. → only seeing it in rat so far
 is started w/ new HPLC system to re-analyse rat & monkey tissue & plasma samples

In Plasma: SIB & sulphonic acid
 In feces - see others

Should I & the protocol to have a w/o for sintonin & anti-coagulants

2nd Meeting

Strategy: Pledge Plan to Kill if Leiden Says ~~No Go~~ No Go

John wants to kill this; ATCO results neutral - negative; No ⊕

Opt 2 Kill - Hard Kill
 Opt 1 Stop everything - try to out-license (sell); keep doing stability, etc; pt clearly continue
 Opt 3 Put it on pause until ???
 Offer pre-emptive plan for development → show how it shows/doesn't show benefit
 Move forward (longi choice)

Put a plan in place - knowing where they are & what we'll do

Augur - Add on to therapy
 Proximal disease vs advanced disease
 ? joint effects?
 Capture non-oncologic indications
 ⊕ how do we study proximal vs advanced

Activity
 If we cut out now - we're already finishing - we put it off
 joint - should answer in Pt I
 prohibit chronic drug administration

Perry wants to give John a worse case now

Activity - Can answer in another Pt I study
 PD → Integrate human tissues in melanoma & head & neck
 Xygonophy - approach

Locally invasive disease
 ACI - BE, PIS, DEIS - early bladder, ...
 entity measured
 Can we work by itself

Page 2

Other possibilitiesNon Cancer :

MS
 Fibrosis — hepatic fibrosis
 polif ~~itis~~ ^{IPF} ^{non-fibrosis} ^{retinopathy}

IPF =
 easy to measure
 very attractive field
 ↓
 "immunology franchise"

Present Plan to John/Jeff now (or May 4, 5th)

Nobody has ever gotten approval
 for locally invasive disease.
 History weak

Marinistat works in MS models. Does ours? Not known.
 Can we do some pre-clinical work?

Steve: will give list of non-cancer to Lopic & Perry to
 build stories for both

Finish Safety Study = \$X spend
 If we move onto later — Gain \$X
 Show Benefit

"Enthusiasm is inversely proportional to knowledge" — Perry

Deposition Exhibit No. 24

P's Exhibit AI

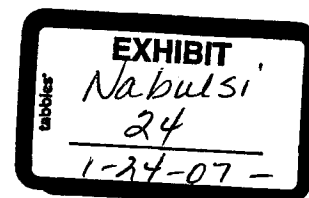
May 01

ABT-518 Matrix Metalloproteinase Inhibitor

Company		Phase I		Phase II		Phase III		Phase IV		Phase V		Phase VI		Phase VII		Phase VIII		Phase IX		Phase X		Phase XI		Phase XII		Phase XIII		Phase XIV		Phase XV		Phase XVI		Phase XVII		Phase XVIII		Phase XIX		Phase XX		Phase XXI		Phase XXII		Phase XXIII		Phase XXIV		Phase XXV		Phase XXVI		Phase XXVII		Phase XXVIII		Phase XXIX		Phase XXX		Phase XXXI		Phase XXXII		Phase XXXIII		Phase XXXIV		Phase XXXV		Phase XXXVI		Phase XXXVII		Phase XXXVIII		Phase XXXIX		Phase XL		Phase XLI		Phase XLII		Phase XLIII		Phase XLIV		Phase XLV		Phase XLVI		Phase XLVII		Phase XLVIII		Phase XLIX		Phase L		Phase LI		Phase LII		Phase LIII		Phase LIV		Phase LV		Phase LVI		Phase LVII		Phase LVIII		Phase LIX		Phase LX		Phase LXI		Phase LXII		Phase LXIII		Phase LXIV		Phase LXV		Phase LXVI		Phase LXVII		Phase LXVIII		Phase LXIX		Phase LXX		Phase LXXI		Phase LXXII		Phase LXXIII		Phase LXXIV		Phase LXXV		Phase LXXVI		Phase LXXVII		Phase LXXVIII		Phase LXXIX		Phase LXXX		Phase LXXXI		Phase LXXXII		Phase LXXXIII		Phase LXXXIV		Phase LXXXV		Phase LXXXVI		Phase LXXXVII		Phase LXXXVIII		Phase LXXXIX		Phase LXXXX		Phase LXXXXI		Phase LXXXXII		Phase LXXXXIII		Phase LXXXXIV		Phase LXXXXV		Phase LXXXXVI		Phase LXXXXVII		Phase LXXXXVIII		Phase LXXXXIX		Phase LXXXXX		Phase LXXXXXI		Phase LXXXXXII		Phase LXXXXXIII		Phase LXXXXXIV		Phase LXXXXXV		Phase LXXXXXVI		Phase LXXXXXVII		Phase LXXXXXVIII		Phase LXXXXXIX		Phase LXXXXXX		Phase LXXXXXI		Phase LXXXXXII		Phase LXXXXXIII		Phase LXXXXXIV		Phase LXXXXXV		Phase LXXXXXVI		Phase LXXXXXVII		Phase LXXXXXVIII		Phase LXXXXXIX		Phase LXXXXXX		Phase LXXXXXI		Phase LXXXXXII		Phase LXXXXXIII		Phase LXXXXXIV		Phase LXXXXXV		Phase LXXXXXVI		Phase LXXXXXVII		Phase LXXXXXVIII		Phase LXXXXXIX		Phase LXXXXXX		Phase LXXXXXI		Phase LXXXXXII		Phase LXXXXXIII		Phase LXXXXXIV		Phase LXXXXXV		Phase LXXXXXVI		Phase LXXXXXVII		Phase LXXXXXVIII		Phase LXXXXXIX		Phase LXXXXXX		Phase LXXXXXI		Phase LXXXXXII		Phase LXXXXXIII		Phase LXXXXXIV		Phase LXXXXXV		Phase LXXXXXVI		Phase 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May 2001

ABT-518

Monthly Highlights - Key Progress

- Decision taken to discontinue Abbott development of Abt-518 due to prioritization. Collaboration or out-license opportunity will be pursued pending favorable safety and PK review of existing patient data.

Key Progress Markers

Key Risks/Issues and Risks

Potential Known Impact	Strategy/Progress	Toxicology/ Metabolism	Resolution
<p>Key risk finding was hepatotoxicity in one-month rat study. <i>In-vitro</i> and <i>In-vivo</i> data indicate a potential for mechanism based drug interactions.</p> <p>Cost Time Profile Regulatory</p>	<p>A 6-week tox and metabolism studies have been completed. Preliminary results show no outward mitochondrial effects. A 3-month rat toxicity study has completed the in-life phase and is under review. All PK analysis will be completed. Histopathology samples will be archived pending collaboration/out-license.</p>	<p>Toxicology/ Metabolism</p>	<p>7/1/01</p>

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ABT-518

<p>Key Project Issues and Risks</p> <p>Cost Time Profile Regulatory</p> <p>Potential or Known Impacts</p> <p>Check for appropriate impact assessment</p>							
<p>Risk/Issue</p> <p>As several competitors are in Phase III, ABT-518 product profile will need to demonstrate advantage over the other compounds (i.e., safety/efficacy)</p>							

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ABT-518

Key Activities

Activity	LBE	Actual
Market research to assess commercial potential of cancer types, both US and Et-US....	4/2001	
Assessment of patient compliance (for revision of forecast)	3/2001	
Assessment of off-label vs. spillover use (for revision of forecasts)	3/2001	
Assessment of cancer market growth (for revision of forecasts)	4/2001	
Assist with advisory planning	4/2001	
Development of brand and generic names	Late 2001	

Activity	Plan	Actual
Phase I Formulation	10/2000	
Phase II Formulation		
Formulation for Bio Study		
Phase III Clinical Supplies Manufactured		
NDA Lot (3) Completed		
Completion of 1 Year Stability for NDA		
Formulation Peer Review		

Activity	KG	Plan	Actual	Actual Projected Costing
Chem Scan (GLP)	3,071.7	6/2000	6/1600	\$133,300
Chem Scan (GLP)	2,021.8	6/2000	6/2800	\$133,300
Chem Scan (GLP)	10.0	6/2001*		
SPD				
SPD				
SPD				
Demo Lot				
NDA Lot #1				
NDA Lot #2				
NDA Lot #3				
Validation Lot				

* Due to program discontinuation - decision may be taken to store a stable intermediate prior to final synthetic step.

Technology Activity	Planned Start Date	Actual Start Date	Report Completed
Gene Toxicology	5/2000		
Acute Studies	5/2000		
2-Week Monkey (non-GLP)	12/1999	12/14/99	
1-Month Rat (non-GLP screening)	12/1999	12/14/99	
1 Month Rat (GLP)	6/2000	6/27/00	
1 Month Monkey (GLP)	6/2000	6/29/00	
3 Month Rat	1/2001	10/01	
3 Month Mouse MTD			
SEG I and SEG II			
SEG III Rat (post natal development)			
6 Month Rat			
1 Year Monkey			
Cardiogenicity (2 yr) Rat			
Cardiogenicity (2 yr) Mouse			

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ABT-518

All Clinical Studies:

Protocol Number	Phase	Study Name	Start 1 st PL Dosed	End (Last CRF In)	Patients		Protocol Number	Phase	Study Name	Start 1 st PL Dosed	End (Last CRF In)	Patients	
					Target	Current						Target	Current
N00-235	I	M0 Study in cancer patients	3/12		40	5							

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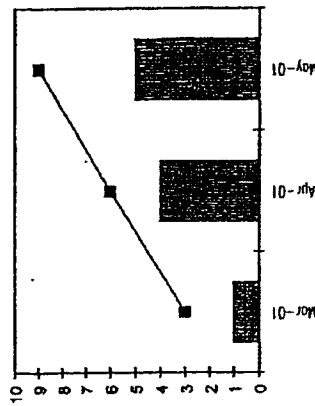
May 2001

ABT-518

Ongoing Clinical Studies (List first time in man, Phase II Dose-Ranging and Pivotal Trials)

Protocol: N00235 Phase I/II in cancer patients
 Objective: Determine MTD and safety profile in cancer patients
 ABT-518 Doses: 25, 50, 100, 200, 400, 800, 1200, 1600, 2000 mg/day
 Comparator Doses: N/A
 Target Enrollment: 40
 Status: 5 patients enrolled to date
 Study Findings: N/A

Enrollment



(Author:
Double click on chart to
edit)

D4772:MPSR\Oncology Group MPSR\May 2001\ABT-518-May01.doc

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Nabulsi Deposition Exhibit 25

D's Exhibit LE



Perry D Nisen

05/20/2001 12:01 PM

To: Azmi A Nabulsi/LAKE/PPRD/ABBOTT@ABBOTT

cc:

cc:

Subject: MMPI

Can you get me a draft (just a few overheads) for MMPI

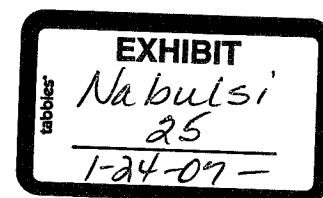
1. summary of ASCO studies

2. status of our program

3. recommendations for our program: where to stop the ph I, partnering, etc
needed by end of day monday if possible

thanks

pn



Confidential
ABBT0064234

Nabulsi Deposition Exhibit 26

P's Exhibit 51

ASCO 2001 MMPI Update

- Ten MMPI abstracts were presented
- Prinomastat, marimastat & Bay 12-9566 reported negative findings
Possible reasons
 - Under dosing due to dose limiting toxicity (joint toxicity)
 - Inappropriate tumor selection
 - Inappropriate tumor stage (late vs. early)
 - Phase II development not done for prinomastat & Bay 12-9566
- BMS 275291 did not show joint toxicity in Phase I. Phase II studies are being initiated in NSCLC & Kaposi's sarcoma



Prinomastat

- Non-small cell lung cancer
 - Combination with paclitaxel & carboplatin
 - No survival benefit
- Hormone refractory prostate cancer
 - Combination with mitoxantrone & prednisone
 - No effects on: PSA, progression free survival, overall survival
- Refractory metastatic breast cancer
 - Phase I/II single agent (n = 44)
- Grade 2 joint toxicity in above trials at all dose levels (5,10,25 mg bid)
- Studies in earlier stage tumors are still ongoing

Marimastat

- Small cell lung cancer
 - Following response to 1st line therapy
 - 10mg vs. placebo
 - Total 155 patients
 - No benefit on progression free survival or overall survival
- Glioblastoma
 - Post surgery & radiotherapy
 - 10mg vs. placebo
 - Total 162 patients
- High dropout rate due to joint toxicity

Bay 12-9566

- Ovarian cancer (stage III or IV)
 - 800mg bid vs. placebo
 - Study was discontinued prior to full enrollment due to lack of activity in pancreatic cancer and SCLC
 - No benefit on survival

BMS 275291

- Phase I studies
 - Healthy volunteers (n = 40 males)
 - Cancer patients (n = 44)
- No joint toxicities (possibly due to lack of sheddase activity)
- No MTD through 2400mg / day
- Phase II plan
 - Non small cell lung cancer in combination with paclitaxel & carboplatin
 - Kaposi's sarcoma
 - Dose 1200 mg / day

**ABT-518 Phase I Multiple-Dose
Study in Cancer Patients
M00-235**

- Patients enrolled to date
 - 25 mg / day 4
 - 50 mg / day $\frac{3}{7}$
- Dosing duration up to 57 days
- Patients will continue dosing until disease progression or adverse events
- No musculoskeletal effects reported to date
- Next dose is 100 mg / day

ABT-518 Development Recommendations

- Continue the ongoing Phase I study

Objectives

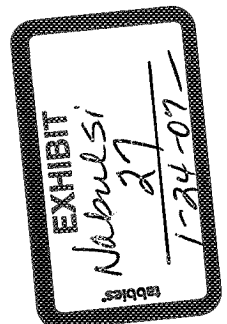
- Determine target dose required to achieve target plasma concentration of 1-3 μ M
 - Assess safety following chronic administration
- Stop development if Grade 3 or 4 toxicities are attributed to doses at or below target dose
- Stop for joint toxicity
- If target dose is well tolerated, initiate a pharmacodynamic/proof of principle study with external funds (e.g., NCI-CRADA) and/or outlicense
 - Biopsy multiple melanoma, head and neck cancer, assay for gelatinase A/B activity

Nabulsi Deposition Exhibit 27

D's Exhibit LF– Part 1

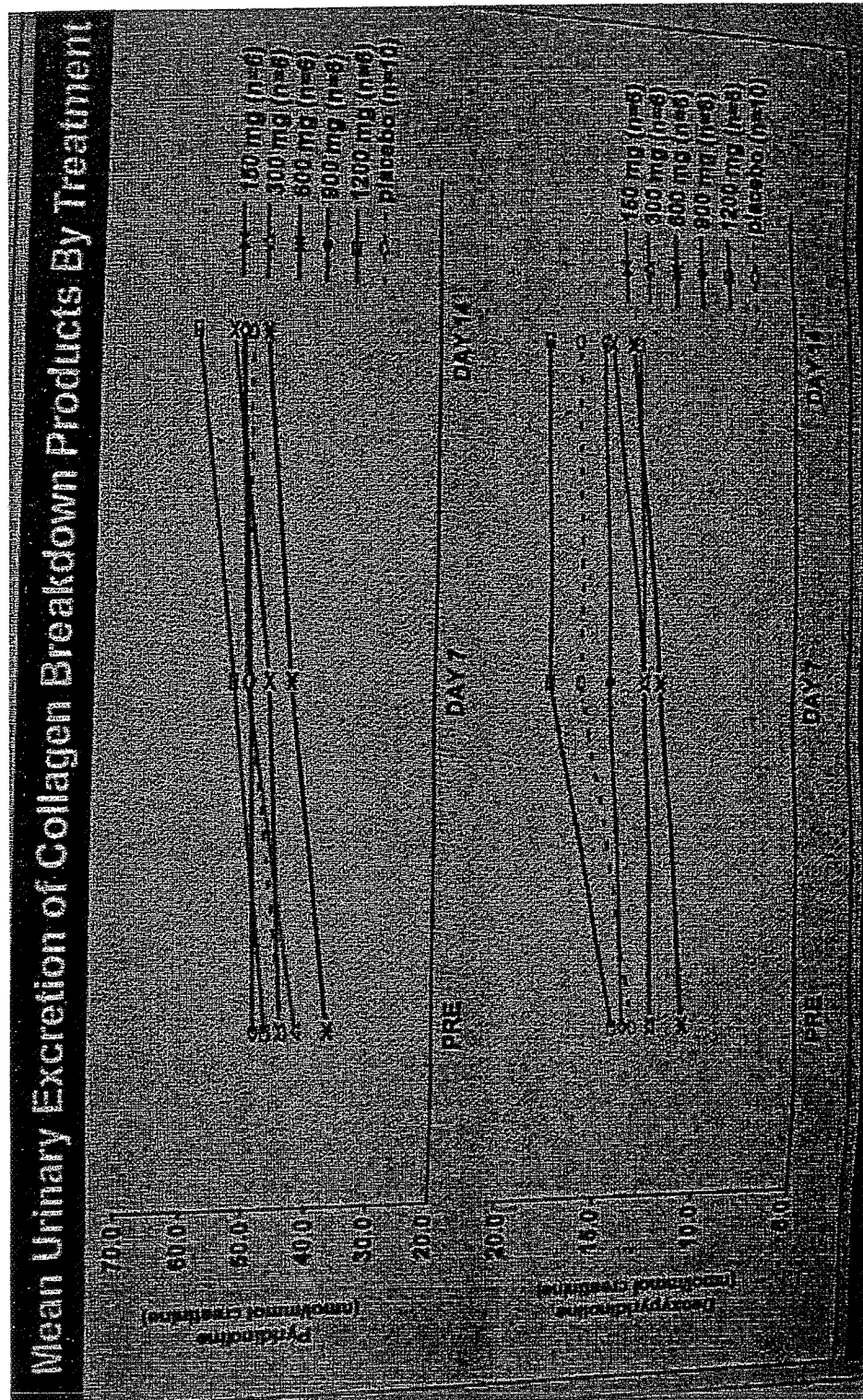
Summary of Healthy Volunteer Data For BMS-275291

- BMS-275291 was safe and very well tolerated in healthy volunteers at doses up to 1200 mg once daily for 14 days; no specific drug-related toxicity evident.
- Cmax and AUC values of unchanged BMS-275291 increased in relation to dose.
- With once daily dosing, little to modest accumulation of unchanged BMS-275291 observed; steady-state achieved by Day 7 of dosing.
- A substantial fraction of "total" BMS-275291 measured in plasma exists in the "unchanged" form.
- No treatment-related decrease in urinary excretion of collagen breakdown products observed with 14-day dosing of BMS-275291.
- Healthy subject data support continued safety and efficacy evaluation of BMS-275291 in patients with cancer.
 - Hurwitz H et al. A phase I trial of BMS-275291, a novel, non-hydroxamate, sheddase-sparing matrix metalloproteinase inhibitor with no dose-limiting arthritis. Proc Am Soc Clin Oncol 20:98a, 2001
 - Gupta E et al. Pharmacokinetic evaluation of BMS-275291, a matrix metalloproteinase inhibitor in cancer patients. Proc Am Soc Clin Oncol 20:76a, 2001.



Nabulsi Deposition Exhibit 27

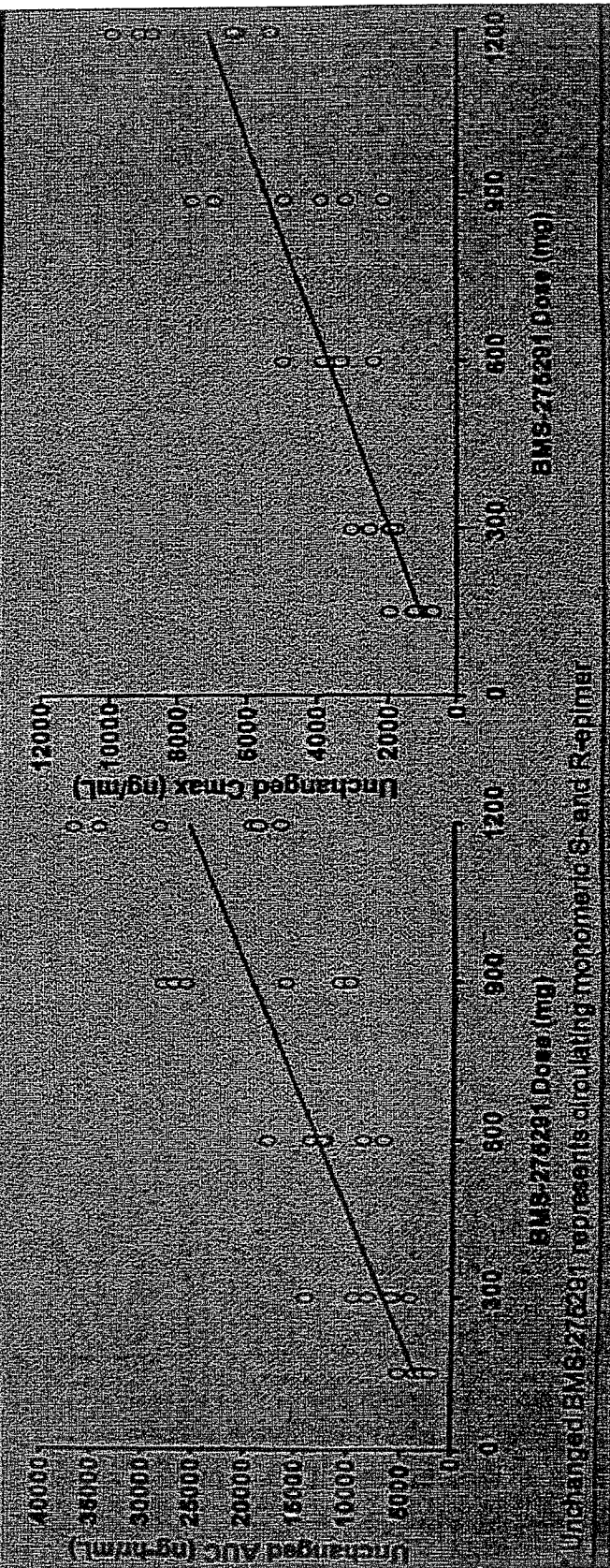
D's Exhibit LF– Part 2



Nabulsi Deposition Exhibit 27

D's Exhibit LF– Part 3

"Unchanged" BMS-275291 Plasma CMAX and AUC Versus Dose on Day 1



Nabulsi Deposition Exhibit 27

D's Exhibit LF– Part 4

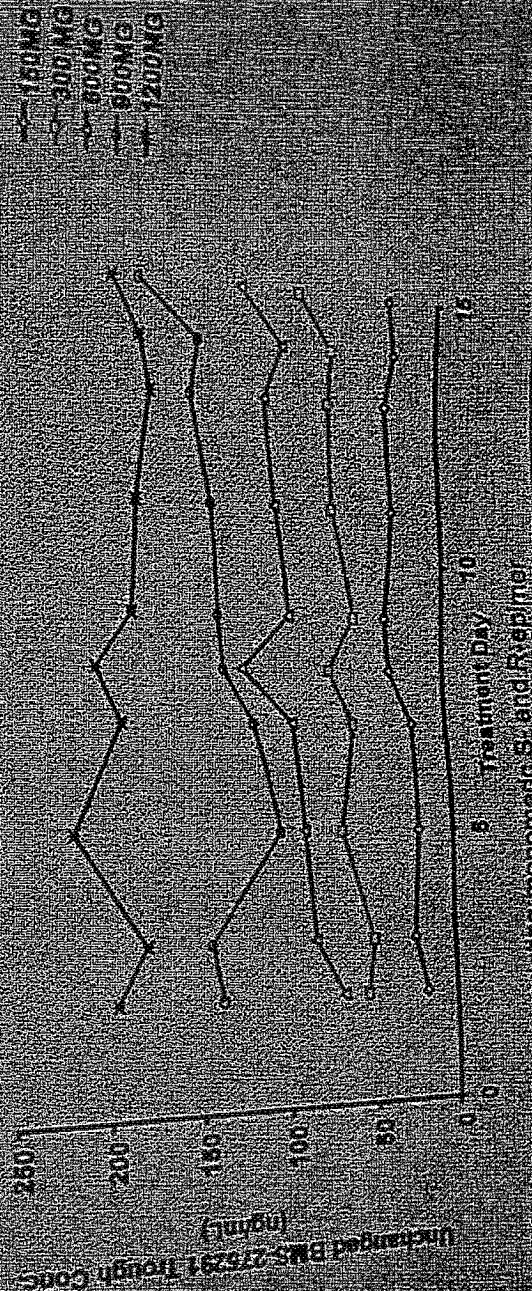
Mean (SD) Plasma PK Parameters for "Unchanged" BMS-275291 on Day 14

Dose (mg)	C _{max} (ng/mL)	AUC(0-24h) (ng·h/mL)	T _{1/2} (h)	Effective T _{1/2} (h)
150	1283 (553)	3680 (1060)	23.1 (12.7)	11.4 (6.3)
300	2561 (1181)	9970 (3948)	38.5 (9.8)	16.3 (4.3)
600	4529 (834)	17110 (4591)	52.6 (12.8)	15.3 (6.8)
900	5348 (1352)	21069 (6860)	44.7 (11.8)	12.7 (4.0)
1200	7160 (1127)	22921 (3300)	47.6 (7.0)	8.6 (1.9)

■ Median (range) T_{max} across all dose levels = 1.0 (0.5-2.0)

* Unchanged BMS-275291 represents circulating monomeric S₁ and R₁-epimer

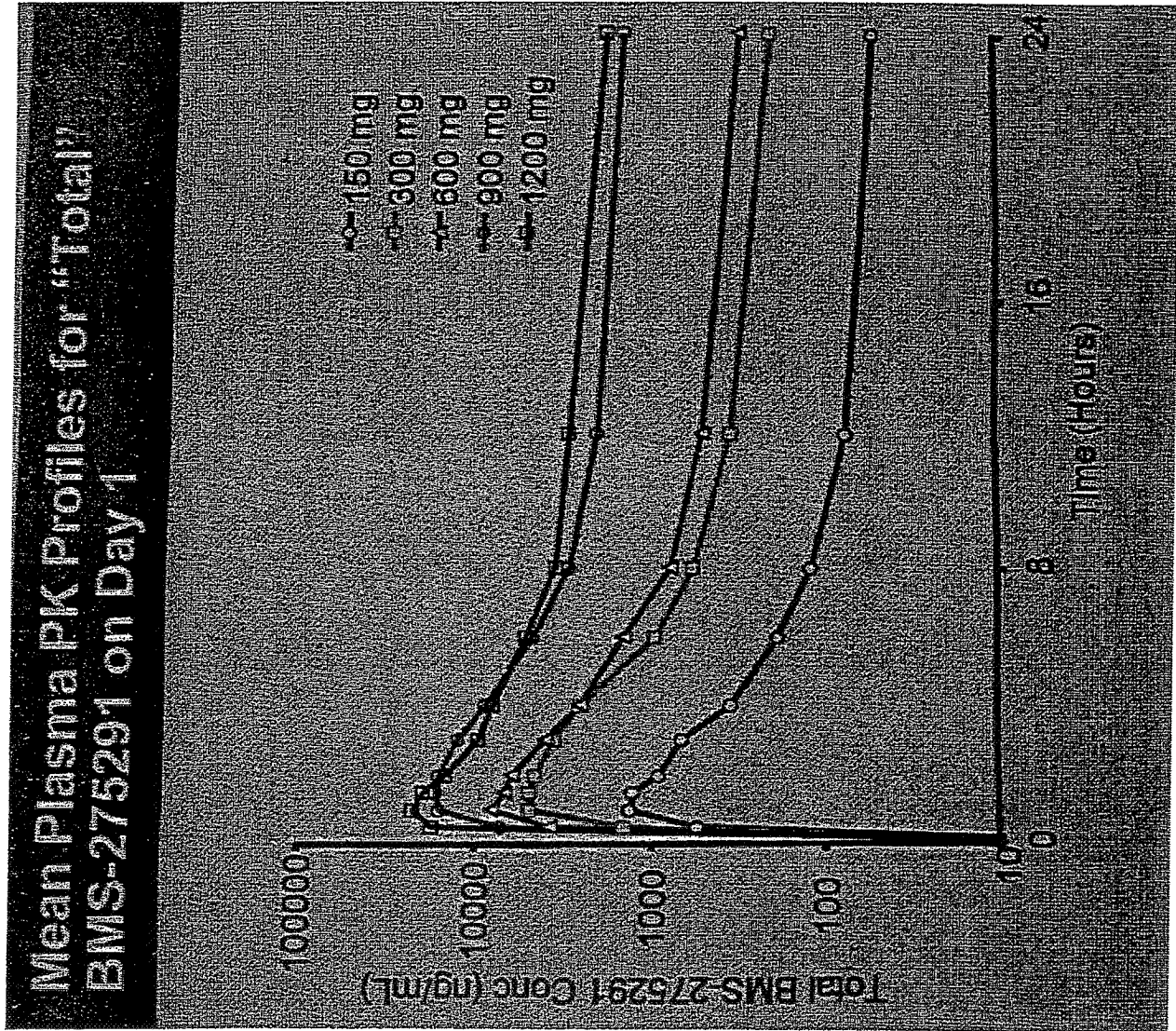
Mean Trough "Unchanged" BMS-275291 Plasma Concentrations by Treatment



* Unchanged BMS-275291 represents circulating monomeric S₁ and R₁-epimer

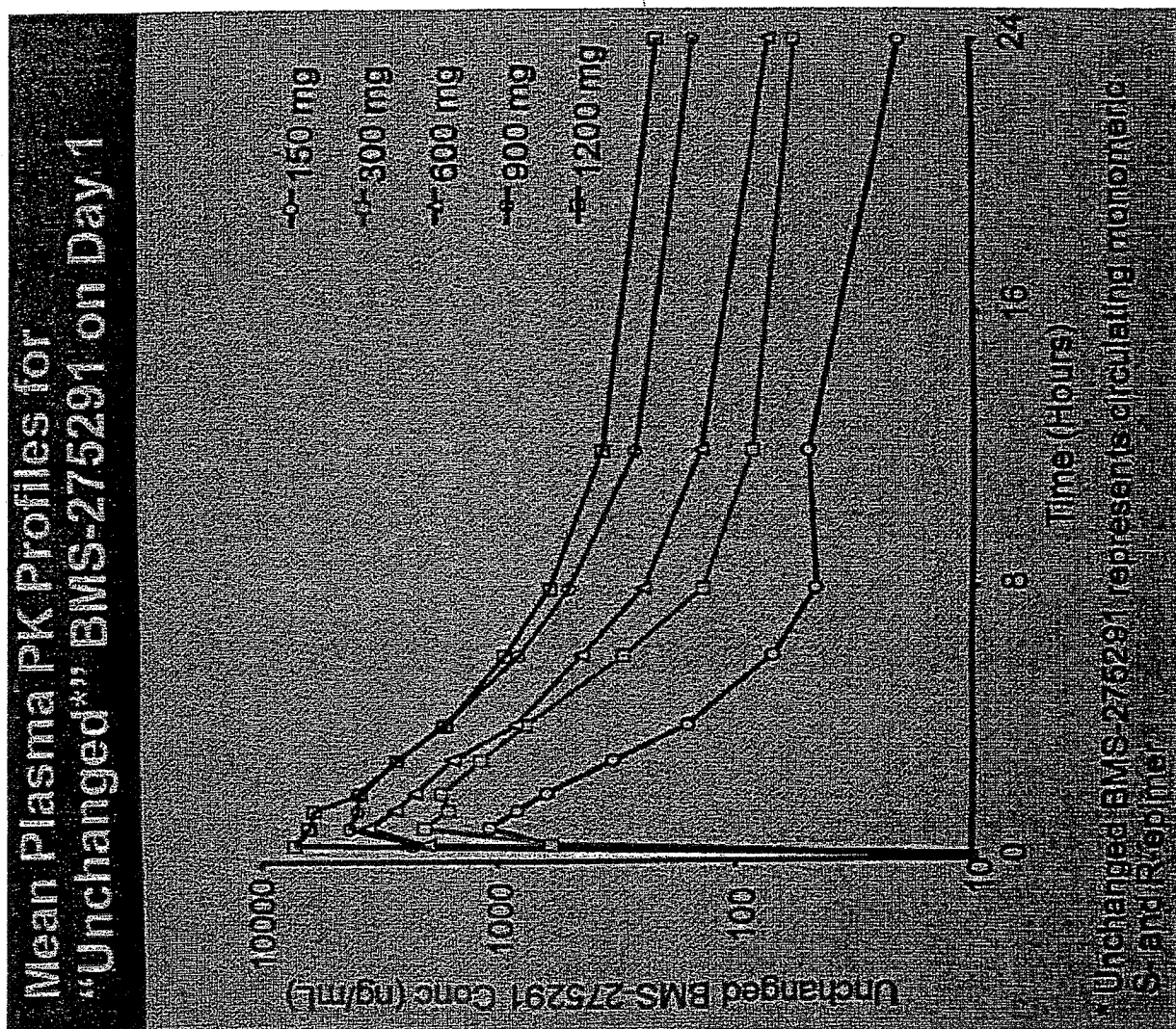
Nabulsi Deposition Exhibit 27

D's Exhibit LF– Part 5



Nabulsi Deposition Exhibit 27

D's Exhibit LF– Part 6



Nabulsi Deposition Exhibit 27

D's Exhibit LF– Part 7

Quantitation of BMS-275291 in Plasma

- Unchanged BMS-275291 (parent R+S-epimer).
- Free sulfhydryl group stabilized with methyl acrylate (MA) to form BMS-275291-MA derivative. Quantitation by on-line extraction followed by LC/MS/MS with positive electrospray detection. Lower limit of quantitation = 10 ng/mL.
- Total BMS-275291 ("unchanged" plus BMS-275291 from reducible disulfides).
- Plasma samples reduced by tris(2-carboxyethyl) phosphine (TCEP), followed by automated 96 well solid phase extraction and quantitation by LC/MS/MS using positive electrospray detection. Lower limit of quantitation = 20 ng/mL.

Multiple Dose Safety of BMS-275291 in Healthy Subjects

- BMS-275291 was very well tolerated in healthy male volunteers.
 - 67% (24/36) of all AEs were mild. The remaining AEs (33%, 12/36) were moderate. No Grade 3 or 4 events.
 - Most frequent AE was mild-moderate headache.
 - Reported by 7/30 (23%) of actively treated and 2/10 (20%) placebo treated subjects.
 - No apparent correlation between number of subjects with AEs and treatment group.
 - 150 mg, 5/6 (83%), 300 mg, 2/6 (33%), 600 mg, 1/6 (17%), 900 mg, 4/8 (57%), 1200 mg, 3/6 (50%) and placebo, 5/10 (50%).
 - No apparent drug-mediated joint toxicity.
 - 2 cases of mild joint toxicity reported (placebo, 1200 mg).

Nabulsi Deposition Exhibit 27

D's Exhibit LF– Part 8

BMS-275291: In Vitro Properties

- Broad spectrum MMP inhibitor

— *In vitro* enzymatic activity of BMS-275291 (S-epimer) determined under reducing conditions

Matrix Metalloproteinase	MMP	IC ₅₀ (ng/mL)
Collagenase-1 (Interstitial)	MMP-1	4.5
Gelatinase A	MMP-2	20.5
Stromelysin-1	MMP-3	78.5
Matrilysin	MMP-7	11.5
Collagenase-2 (neutrophil)	MMP-8	5.0
Gelatinase B	MMP-9	12.5
Collagenase-3	MMP-13	2.0
MT1-MMP	MMP-14	20.0

- Does not inhibit sheddase activities

— Using *in vitro* cell-based assays the IC₅₀s for release of TNF- α , TNF-R II, L-Selectin, IL-1, IL-6-R were all > 50,000 ng/mL

— Cells treated with mitogen in the presence of BMS-275291 and the cell-associated mitogen release in the medium measured by ELISA

Multiple Dose Escalation Study Design

- Randomized, double-blind, placebo-controlled, multiple-dose, dose escalation trial in healthy male subjects

- 14-day dosing evaluating once daily dosing

— 150 mg, 300 mg, 600 mg, 900 mg & 1200 mg

- PK on Day 1, Day 7 and Day 14

— "Unchanged" BMS-275291 = monomeric BMS-275291 (R + S epimer)

— "Total" BMS-275291 = total reducible BMS-275291

- Evaluate effects of BMS-275291 on urinary excretion of collagen breakdown products (pyridoline, deoxypyridinoline)

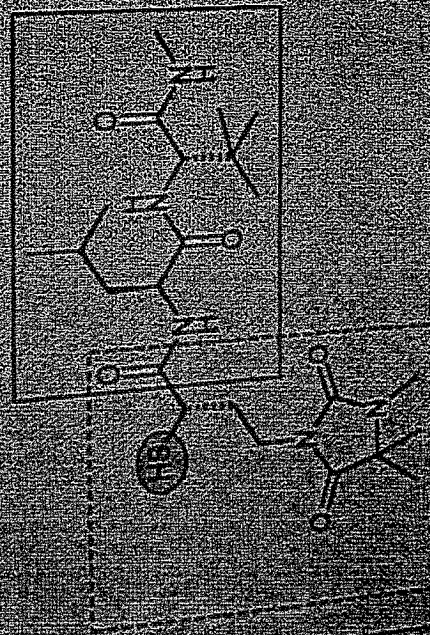
Nabulsi Deposition Exhibit 27

D's Exhibit LF– Part 9

BMS-275291: Matrix Metalloproteinase Inhibitor

- Broad spectrum inhibitor of matrix metalloproteinases including MMP-1, MMP-2 and MMP-9
- Rationally designed to avoid muscle/joint toxicity of earlier drugs in this class selectively for MMPs versus membrane secretases (shedases)
- Single-dose, dose escalation trial in healthy subjects demonstrated good safety and tolerability profile; doses evaluated were 25, 75, 150, 300, 600 & 900 mg
- Potential for once daily, oral outpatient regimen with no dose-limiting arthritis

BMS-275291



- Contains a mercaptoamide zinc binding group
- Due to the presence of a free sulphydryl group, BMS-275291 can readily form disulfides with other sulphydryl compounds
- Undergoes epimerization *in vivo*; mixture of active S-epimer and 60-fold less potent R-epimer detected in plasma
- Monomeric, S-epimer of BMS-275291 is believed to be the principal active species

Nabulsi Deposition Exhibit 27

D's Exhibit LF– Part 10

ASCO2001 395


Abstract

BMS-275291 is a novel, non-hydroxamate matrix metalloproteinase inhibitor (MMPi) prospectively designed to inhibit a broad spectrum of MMPs (including MMP-2 and MMP-9) and spare sheddases (related metalloproteinases). Sheddase inhibition is hypothesized to play a major role in the dose-limiting arthritis noted for hydroxamate-based MMPi's. To investigate the multiple-dose safety and pharmacokinetics (PK) of BMS-275291 in healthy subjects, a randomized, double-blind, placebo-controlled dose-escalation study was conducted. Forty males were randomly enrolled in cohorts of 8 and received either BMS-275291 or placebo (6 active and 2 placebo) once daily for 14 days. Daily BMS-275291 doses were 150, 300, 600, 900 and 1200 mg. Due to the presence of a free sulfhydryl group, BMS-275291 is able to form disulfides with other sulfhydryl-containing molecules *in vivo*. LC/MS/MS and LC/MS assays were developed to quantitate both parent and total (parent plus all reducible disulfides) BMS-275291 in plasma, respectively. Treatment with BMS-275291 was safe and very well tolerated across all dose levels. No dose-limiting adverse events were identified. Mild to moderate headache was reported in 20% of subjects; however, this incidence was similar for placebo and treated subjects. Two subjects (1 active, 1 placebo) reported mild myalgia and/or arthralgia. Plasma exposures of parent BMS-275291 (C_{max} and AUC) increased in relation to dose. Little to modest accumulation of parent BMS-275291 was observed; steady-state was reached by Day 7. Total BMS-275291 plasma exposures appeared to increase disproportionately higher than the dose increase. At all doses, average steady state trough plasma concentrations of parent BMS-275291 exceeded the IC_{50} values for MMP-2 (20 ng/mL) and MMP-9 (14 ng/mL). No apparent treatment-related effects on the urinary excretion of collagen breakdown products (pyridoline, deoxypyridine) were noted. These data in healthy subjects support the continued safety and efficacy evaluation of BMS-275291 in patients with cancer.

ABBT0556330

Nabulsi Deposition Exhibit 27

D's Exhibit LF– Part 11

Meeting: 23rd ASCO Annual MeetingCategory: Lung CancerSubCategory: Non-Small-Cell Lung Cancer Primer Finding Bookmark**Phase III Study of the Matrix Metalloprotease (MMP) Inhibitor Prinomastat in Patients Having Advanced Non-Small Cell Lung Cancer (NSCLC).**

Abstract No: 1726



Author(s): Michael Smylie, Richard Mercier, David Aboulafia, Robert Tucker, Philip Bonomi, Mary Collier, Mary Rose Keller, Jill Stuart-Smith, Mark Knowles, Neil J. Clendenen, Frances Sheehar, Cross Cancer Institute, Edmonton, Canada; Marshfield Clinic, Marshfield, WI; Virginia Mason Medical Center, Seattle, WA; Wake Forest University, Winston Salem, NC; Rush University, Chicago, IL; Agouron Pharmaceuticals Inc, A Pfizer Company, La Jolla, CA; Princess Margaret Hospital, Toronto, Canada.

Abstract: MMPs degrade extracellular proteins, facilitating tumor invasion, angiogenesis, and metastasis. Prinomastat (AG3340) is a potent inhibitor of MMPs that demonstrated efficacy in in vivo tumor models. A phase III study investigated prinomastat in combination with paclitaxel (P) and carboplatin (C) in chemotherapy naive patients (pts) having NSCLC. P (200 mg/m² over 3 hours) and C (AUC6) were administered q3 weeks. Pts were randomized to prinomastat 5mg (dose ranging arm), 10mg or 15mg, or placebo, orally twice daily. Between 3/98 and 9/99, 686 pts were enrolled; interim results are available for 677 pts. Baseline characteristics were balanced with median age 62 years, 62% male, 85% WHO PS 0-1, 56% adenocarcinoma, 12.6% stage IIIB(T4), 74% stage IV, 11.8% recurrent disease, and 84% measurable disease. P+C dose intensity and toxicity were comparable among the treatment arms. Musculoskeletal effects (MS, hypothesized to be related to MMP inhibition) were the only adverse experiences having time- and dose-relationship to prinomastat. Symptoms included arthralgia, joint stiffness and swelling and rarely, tendinous contracture. Grade 2 events occurred in 16, 19, 22 and 31% of pts in placebo, 5, 10 and 15mg arms, respectively. Grade 2 MS persisting for 3 weeks were managed by treatment rest and prinomastat dose reduction. No differences were observed among the treatment arms in overall (OS) or 1-year survival, progression-free survival (PFS), symptomatic PFS (SPFS) or response rate (RR). Efficacy was not enhanced by the addition of prinomastat to P+C in pts having advanced NSCLC.

Efficacy Parameters

	Patients	RR	Median (months)			1-Yr Survival
	Randomized	%	PFS	SPFS	OS	%
P+C- Placebo	198	21	3.5	6.3	10.2	29
P+C- 5mg	84	27	3.6	5.3	9.3	30
P+C- 10mg	197	19	3.3	5.1	8.6	35
P+C- 15mg	198	18	4.3	6.2	9.1	40

Meeting: 2007 ASCO Annual Meeting
 Category: Breast Cancer
 SubCategory: Metastatic Breast Cancer

 [Print Friendly](#)
 [Bookmark](#)

Phase II Study of the Matrix Metalloprotease Inhibitor Prinomastat in Patients with Progressive Breast Cancer.

Abstract No: 187

Author(s): Hope S. Rugo, Dan Budman, Charles Vogel, Said Baidsa, Gini Fleming, Mary Collier, Mary Dixon, Farid Pithavala, Neil J. Clendenning, Teju Tripathy, Ean Hayes, University of California San Francisco, San Francisco, CA, North Shore University Hospital, Manhasset, NY, Columbia Cancer Research Network, Plantation, FL, Lombardi Cancer Center, Georgetown University, Washington, DC, University of Chicago, Chicago, IL, Amgen Pharmaceuticals Inc, A Pfizer Company, La Jolla, CA

Abstract: Matrix metalloproteases (MMPs) are enzymes that degrade the extracellular matrix. Prinomastat (AG3340) is a potent MMP inhibitor designed using X-ray crystallography that reduced tumor angiogenesis, invasion, and metastasis in preclinical models. Patients (pts) having metastatic breast cancer that progressed on most recent therapy were randomized to 5 or 25 mg prinomastat administered orally twice daily. The rate of stable disease (SD), time to progression (TTP), potential biomarkers of MMP inhibition and the safety of single agent prinomastat were studied. 15 pts were to enroll into each treatment arm with expansion to 30 pts in an arm if at least one pt had SD at 8 weeks. A total of 44 female pts were enrolled; 29 pts received 5 mg and 15 pts received 25 mg prinomastat. Median age was 58 years (range 37-84), 93% of pts had failed chemotherapy in the metastatic setting, 55% had visceral metastases, and 70% had measurable disease. Musculoskeletal effects (hypothesized to be related to MMP inhibition) required treatment rest or discontinuation in 21% of pts at 5 mg between weeks 8-24 and 27% of pts at 25 mg between weeks 4-8. No objective disease responses were observed. Median TTP was 8 weeks in both arms, 9/29 pts in the 5 mg dose arm had SD at week 8, with 5 pts stable for at least 16 weeks. Preliminary analyses indicate that some biomarkers had potential prognostic value or paralleled disease progression. Low pretreatment plasma VEGF (<40 pg/mL) and urine pyridinoline levels (<90 pmol/[micro]mol creatinine) correlated with SD at 8 weeks [67% vs 25% ($p<0.05$), and 100% vs 42% ($p<0.005$) for SD vs PD at week 8, respectively]. Further analyses of disease stabilization and correlative studies will be presented.

Meeting: 2001 ASCO Annual MeetingCategory: Genitourinary CancerSubCategory: Prostate Cancer Printer-friendly Bookmark

Interim Results of a Phase III Study of the Matrix Metalloproteinase Inhibitor Prinomastat in Patients Having Metastatic, Hormone-Refractory Prostate Cancer (HRPC)

Abstract No: 692

Author(s): Frederick R. Ahmann, Fred Sand, Richard Marner, Robert A. Huddart, J. Trevor Roberts, Mary Collier, Lei-Anna Bettencourt, Min H Zhang, Neil J. Clendeninn, George Wilding, Arizona Cancer Center, Tucson, AZ; CHUM-Notre Dame, Montreal, Canada; Marshfield Clinic, Marshfield, WI; The Royal Marsden, Sutton, UK; Newcastle General Hospital, Newcastle, UK; Agouron Pharmaceuticals Inc., A Pfizer Company, La Jolla, CA; University of Wisconsin, Madison, WI

Abstract: Matrix metalloproteinases (MMPs) degrade extracellular proteins, facilitating tumor invasion, angiogenesis, and metastasis. Prinomastat (AG-3340) is a potent inhibitor of MMPs that demonstrated efficacy in preclinical in vivo tumor models. A phase III trial investigated prinomastat in combination with mitoxantrone (M) and prednisone (P) in chemotherapy-naïve patients (pts) having metastatic HRPC. M was administered intravenously at 12 mg/m² q3weeks and P orally, 5mg twice daily. Pts were randomized to 5 or 10mg prinomastat or placebo, orally twice daily. Between 4/98 and 7/01, 553 pts were enrolled; interim results are available for 406 pts. Baseline characteristics were balanced with median age 71 years, median PSA 84 ng/mL, and 33% measurable disease. M+P dose intensity and toxicity were comparable among the treatment arms. Musculoskeletal effects (MS, hypothesized to be related to MMP inhibition) were the only adverse experiences having time- and dose-relationship to prinomastat. Symptoms included arthralgia, joint stiffness and swelling and rarely, tendinous contracture. Grade 2 MS were observed in 13, 22 and 22% of pts in the placebo, 5 and 10mg arms, respectively; events persisting for at least 3 weeks were managed by treatment rest and prinomastat dose reduction. No differences were observed among the treatment arms in PSA response rate (RR, 75% reduction for 3wks), progression-free survival by radiography (RPFS), PSA (50% increase for 3wks), or symptoms (SPFS), or overall (OS) and 1-year survival. Efficacy was not enhanced by the addition of prinomastat to M+P in pts having metastatic HRPC.

Efficacy Parameters

	Patients	PSA/RR	Median (months)				1-Year Survival
	Randomized	(%)	RPFS	PSA/PFS	SPFS	OS	(%)
M+P	138	14	6.0	6.8	7.7	14.8	60

M+P- 5mg	134	17	6.0	8.9	8.6	15.1	64
M+P-	134	18	4.7	6.5	8.3	14.7	63

Nabulsi Deposition Exhibit 27

D's Exhibit LF– Part 12

Meeting: 2001 ASCO Annual Meeting
 Category: Gynecologic Cancer
 SubCategory: Gynecologic Cancer

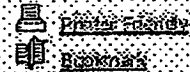
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An International Multicentre Phase III Study of BAY 12-9566 (BAY) Versus Placebo in Patients (pts) with Advanced Ovarian Cancer (OVCA) Responsive to Primary Surgery/Paclitaxel + Platinum Containing Chemotherapy (CT):

Abstract No: **543**

Author(s): Hal W. Hirtle, Ignace B. Vergote, John R. Jeffery, Robert N. Grisham, Gavin C. Stuart, Cesar Vendicola, Daniel A. Yee, Mark S. Carey, Sabine Coigniet, Brian Schwartz, Dongsheng Tu, Anne Sartre, Lesley Seymour, Hamilton Regional Cancer Centre, Hamilton, ON, Canada; University Hospital Leuven, Leuven, Belgium; Health Sciences Centre, University of Manitoba, Winnipeg, MB, Canada; Nova Scotia Cancer Centre, Halifax, NS, Canada; Tom Baker Cancer Centre, Calgary, AB, Canada; Hospital Universitaria, Madrid, Spain; Sandton Oncology Centre, Johannesburg, South Africa; London Regional Cancer Centre, London, ON, Canada; Bayer s.a. - n.v., Bruxelles, Belgium; Bayer Inc., Toronto, ON, Canada; National Cancer Institute of Canada - Clinical Trials Group, Kingston, ON, Canada; National Cancer Institute of Canada - Clinical Trials Group, Kingston, ON, Canada.

Abstract: BAY is a biphenyl matrix metalloproteinase inhibitor (MMPi) with anti-angiogenic and anti-metastatic properties in vivo. The objective of the study was to determine whether the addition of BAY after optimal response to chemotherapy could improve survival. Pts enrolled in the study had received 6-9 cycles of platinum/paclitaxel containing CT for stage III or IV OVCA, with a response of NED, or complete or partial response with residual disease ≤ 2 cm. Pts were then randomized to BAY 800 mg po bid or placebo. The primary endpoint was progression-free survival (PFS), secondary endpoints were quality of life, toxicity, response, and overall survival (OS). The total planned sample size was 780. The study was closed after 243 pts had been randomized because of negative results from other phase III trials in pancreatic and small cell lung cancer. The final analysis was performed in August 2000 after the requisite number of events for the first planned IA had occurred; 54% of patients had progressed and 18% had died. Patient characteristics: performance status was ECOG 0/1/2 in 65/33/2%; median age 57 years; 80% of pts were FIGO stage III; 60% were optimally debulked; 76% had serous histology and 66% had grade 3 histology. Toxicity was generally grade 1 or 2 in severity, with the most common (BAY versus placebo) being nausea (26% versus 13%), fatigue (34% versus 12%), diarrhea (14% versus 10%), rash (12% versus 7%), grade 3/4 thrombocytopenia (3% versus 1%) and grade 3/4 anemia (5% versus 1%). PFS was 10.4 months (3.5-11.5) for BAY and 9.2 months (7.2-13.0) for placebo ($p=0.67$). OS was 13.9 months (12.9-[infinity]) for BAY and 11.9 months (10.5-16.5) for placebo ($p=0.53$). We conclude that BAY was generally well tolerated and although the data are still immature, there is no evidence of an impact of BAY on PFS or OS.

Meeting: 2001 ASCO Annual MeetingCategory: Lung CancerSubCategory: Small Cell Lung Cancer

Randomized Double-Blind Placebo-Controlled Trial of Marimastat in Patients with Small Cell Lung Cancer (SCLC) Following Response to First-Line Chemotherapy: an NCIC-CTG and EORTC Study.

Abstract No: 11

Author(s): Frances A. Shepherd, G. Giaccone, C. Hahn, V. Hirsh, A. Smylie, S. Rubin, H. Martins, A. Lamer, M. Krzakowski, B. Zee, A. Sadura, L. Seymour, National Cancer Institute of Canada Clinical Trials Group, Toronto, ON, Canada.

Abstract: Increased expression of matrix metalloproteinases is associated with poor prognosis in SCLC. Marimastat (M) is an orally available, broad-spectrum matrix metalloproteinase inhibitor that has shown pre-clinical activity in many solid tumors. This trial was undertaken to determine whether adjuvant treatment with M could prolong remission duration and overall survival in patients with SCLC. Patients with documented SCLC and performance status 0-2 were eligible for study if they had achieved CR or PR in response to 1st-line therapy and had life expectancy ≥ 12 wks. They were stratified by radiotherapy (early vs late, vs none), stage at diagnosis (extensive vs limited) response (CR vs PR) and cooperative group. They were randomized to receive M 10 mg po bid or placebo 1 capsule po bid for up to 2 yrs. Treatment was stopped for disease progression or toxicity. The study has 80% power to detect a 33% improvement in survival using a 2-sided test. Between 2/97 and 4/00, 555 patients entered the trial. The median duration of follow-up is 20.4 mos and all patients have completed at least 8 mos treatment or have discontinued therapy due to toxicity or relapse. Toxicity was generally limited to musculoskeletal (MS) syndromes (Grade 2, 31%; Grade 3/4, 12%). Dose modifications for MS toxicity were required in 113 patients (20%), and 128 patients (23%) permanently stopped protocol therapy due to toxicity (104 of the 128 stopped for MS toxicity). The median survival for the entire group is 9.5 mos, with 1-yr and 2-yr survivals of 38% and 20% respectively. Survival according to treatment group will be available by May 2001.

PATIENT CHARACTERISTICS

	MARIMASTAT (n=277)	PLACEBO (n=278)
NCIC/EORTC	209/68	211/67
Male/Female	164/133	147/131
Age (median)	61.6 years	61.2 years
Limited/Extensive	146/131	137/141
CR/PR/Other	90/174/13	90/184/4

Updated data not available through ASCO abstracts. Study was published; see JCO abstract below.

1: J Clin Oncol. 2002 Nov 15;20(22):4434-9.
<http://www.jco.org/cgi/content/full/20/22/4434>

Prospective, randomized, double-blind, placebo-controlled trial of marimastat after response to first-line chemotherapy in patients with small-cell lung cancer: a trial of the National Cancer Institute of Canada-Clinical Trials Group and the European Organization for Research and Treatment of Cancer.

Shepherd FA, Giaccone G, Seymour L, Debruyne C, Bezjak A, Hirsh V, Smylie M, Rubin S, Martins H, Lamont A, Krzakowski M, Sadura A, Zee B.
National Cancer Institute of Canada-Clinical Trials Group.
frances.shepherd@uhn.on.ca

PURPOSE: Increased expression of metalloproteinases is associated with poor prognosis in small-cell lung cancer (SCLC). This trial was undertaken to determine whether adjuvant treatment with the metalloproteinase inhibitor marimastat could prolong survival in responding patients with SCLC after chemotherapy. **PATIENTS AND METHODS:** SCLC patients in complete or partial remission were eligible. They were stratified by radiotherapy (early, late, or none), stage (extensive or limited), response (complete or partial), and cooperative group (National Cancer Institute of Canada-Clinical Trials Group or European Organization for Research and Treatment of Cancer). They were randomized to receive marimastat 10 mg or placebo orally bid for up to 2 years. **RESULTS:** There were 532 eligible patients (266 marimastat and 266 placebo). Stage was limited for 279 patients (52%) and extensive for 253 (48%). Best response to induction therapy was complete remission for 176 patients (33%), partial remission for 341 (64%), and 15 patients (3%) had undergone surgical resection. The median time to progression for marimastat patients was 4.3 months compared with 4.4 months for placebo patients ($P = .81$). Median survivals for marimastat and placebo patients were 9.3 months and 9.7 months, respectively ($P = .90$). Toxicity was generally limited to musculoskeletal symptoms (18% grade ≥ 3 for marimastat). Dose modifications for musculoskeletal toxicity were required in 90 patients (33%) on the marimastat arm, and 87 (32%) permanently stopped marimastat because of toxicity. Patients on marimastat had significantly poorer quality of life at 3 and 6 months. **CONCLUSION:** Treatment with marimastat after induction therapy for SCLC did not result in improved survival and had a negative impact on quality of life.

PMID: 12431965 [PubMed - indexed for MEDLINE]

ASCO 5-01

Phase II Study of the Matrix Progressive Breast Cancer

I Rugo¹, D Tripathy¹, D Budman², C Vogel³, S Baidas⁴, G Fleming⁵, M Collier⁶, M Dixon⁶, Y Pithavala⁶, NJ Clendeninn⁶University of Chicago, Chicago, IL⁵; Agouron Pharmaceuticals Inc, A Pfizer Company, La Jolla, CA⁶.

Updated Abstract

Matrix metalloproteinases (MMPs) are enzymes that degrade the extracellular matrix. Prinomastat (AG3340) is a potent MMP inhibitor designed using x-ray crystallography that reduced tumor angiogenesis, invasion, and metastasis in preclinical models. Patients (pts) having metastatic breast cancer that progressed on most recent therapy were randomized to 5 or 25 mg prinomastat administered orally twice daily (BID). The rate of stable disease (SD), time-to-progression (TTP), potential biomarkers of MMP inhibition, and the safety of single-agent prinomastat were studied. 15 pts were to enroll in each treatment arm with expansion to 30 pts in an arm if at least one pt had SD at 8 weeks (wks). A total of 44 female pts were enrolled, 29 pts received 5 mg and 15 pts received 25 mg prinomastat. Median age was 59 years (range 37-84), 93% of pts had failed chemotherapy in the metastatic setting, 3% had visceral metastases, and 71% had measurable disease. Musculoskeletal effects (hypothesized to be related to MMP inhibition) required treatment discontinuation in 28% of pts at 5 mg between wks 8-24 and 33% of pts at 25 mg between wks 4-20. No objective disease responses were observed. Median TTP was approximately 8 wks in both arms, 9/29 pts in the 5 mg dose arm had SD at wk 8, with 7 pts stable for at least 16 wks. At wk 8 was observed in 1/15 pts in the 25 mg dose arm, however, the arm was not expanded because of minimal activity and joint toxicity. Preliminary analyses indicate that some biomarkers had potential prognostic value or paralleled disease progression. Baseline values for plasma VEGF, and urinary markers N-telopeptide, deoxypyridinoline, and pyridinoline were significantly different in SD versus PD patients at wk 8 ($P < 0.05$). Additionally, the absolute change from baseline at wk 8 in plasma TIMP-1 levels was lower in SD pts versus PD pts ($P = 0.029$). No significant differences were observed for MMP-9, bone-specific alkaline phosphatase, and HER-2/neu levels in plasma.

Background

Matrix Metalloproteinases (MMPs):

- Family of at least 20 enzymes that degrade extracellular matrix (ECM) proteins
- Produced by tumor cells and normal host stromal cells
- Expressed in response to cytokines, growth factors, or changes in cell-cell or cell-ECM interactions

MMPs and Cancer:

- Deregulation of MMPs promotes cancer
 - tumor invasion
 - metastasis
 - angiogenesis
 - signaling processes that favor tumor cell survival
- Over expression of selected MMPs correlates with poor prognosis
- MMPs 2, 3, 9, and 14 implicated in cancer

Prinomastat (AG3340):

- Potent inhibitor of MMPs 2, 3, 9, 13 and 14, less potent inhibitor by design for MMP 1 (MMP hypothesized to be responsible for joint effects)
- Preclinical models
 - broad antitumor activity (including 2 human breast cancer xenograft models)
 - shown to inhibit tumor invasion, angiogenesis and metastasis
- Clinical pharmacology
 - pharmacokinetics (PK) linear over 2mg-100mg BID range
 - plasma free fraction = 11%
 - dose-related joint effects are mechanism based, used as a marker of MMP inhibition
- Clinical activity (single-agent phase I study)
 - 16 of 75 patients with heavily pretreated solid tumors experienced stable disease for at least 16 wks
 - evidence of minor tumor reduction observed in 3 patients (melanoma, NSCLC, and renal cell)

Study Objectives

Determine:

- % of patients having progressive breast cancer who experience disease stabilization (SD) or improvement ≥ 8 wks
- Progression-free survival
- Effect of prinomastat on biomarkers in the blood and urine
- Safety

Patients and Methods

Eligibility Criteria

- WHO PS 0-2
- Histologically confirmed metastatic breast cancer
- Disease progression during or following most recent therapy
- Brain metastases without evidence of progression ≥ 3 months since radiation or surgery allowed
- No chemotherapy, biological agents or hormone therapy in previous 2 wks
- No changes in bisphosphonate regimen in last 3 months
- Informed consent

Study Design

- Randomized, double-blind, dose-controlled
- 2 treatment arms: 5 or 25 mg prinomastat BID (BID)
- 2-stage design
 - stage I: 15 patients per treatment arm
 - stage II: if 1/15 achieve SD or improving disease at wk 8, arm expanded by 15 patients
- total N: between 30 and 60 patients
- After progression, continuation of prinomastat with subsequent therapy allowed

Treatment

- Starting dose, 5 or 25 mg prinomastat BID
- Treatment rest and dose reduction for patients having grade 2 joint effects persisting for 3 wks
- Dose reduction schema: 25 mg BID → 5 mg BID → 2.5 mg BID (lowest dose)

Biomarkers

Measured in Blood/Plasma or Serum:

- vascular endothelial growth factor (VEGF)¹
- MMP 3 and 9²
- tissue inhibitor of MMP 1 (TIMP 1)³
- bone-specific alkaline phosphatase⁴
- N-telopeptide and deoxypyridinoline⁵
- extracellular domain of HER-2/neu⁶

Measured in Whole Blood:

- number of circulating epithelial cells

Measured in Urine:

- N-telopeptide¹
- deoxypyridinoline¹
- pyridinoline¹

¹Performed at Quest Diagnostics, San Juan Capistrano, CA

²Performed at M.S. Hershey Medical Center, Department of Pathology and Laboratory Medicine, Hershey, PA

- Measured twice at baseline, every 2 wks through wk 16, and every 4 wks thereafter until progression
- Absolute baseline biomarker values and change in biomarker values at wk 8 were correlated with disease status at wk 8 (stable disease versus progressive disease)

Pharmacokinetics

Table 5: Prinomastat Steady-state Plasma PK Parameters (Week 6)

	5 mg BID		25 mg BID	
	SD ^a at wk 8 (n=9)	PD ^b at wk 8 (n=10)	SD ^a at wk 8 (n=10)	PD ^b at wk 8 (n=10)
C _{min} (trough concentration), ng/mL	2.8 ± 2.0	2.6 ± 2.0	NA ^c	19.8 ± 32.6
C _{max} (peak concentration), ng/mL	155 ± 108	131 ± 79		595 ± 420
T _{max} (time of peak concentration), hr	1.1 ± 1.0	0.5 ± 0.0		1.2 ± 0.9
AUC ₀₋₂₄ ng·hr/mL	243 ± 126	222 ± 137		1063 ± 559

^aData from a phase I dose-escalation study (study AG3340-003) of single-agent prinomastat on day 29, in patients with advanced cancer

^bSD=stable disease, PD=progressive disease

^cPK plasma samples not collected from the only subject with SD at wk 8 in the 25 mg BID arm

- Prinomastat PK parameters for both dose groups were comparable to historical estimates in advanced cancer patients

Safety

Table 6: Toxicity Profile Single-agent Prinomastat N=44

Event	5 mg BID (n=29)			25 mg BID (n=15)		
	All Grades	No.	%	All Grades	No.	%
Arthralgia	9	31	2	10	67	3
Back pain	3	10		1	7	1
Joint stiffness	4	14		5	33	2
Musculoskeletal pain	1	3		2	13	
Altered taste				3	20	
Nausea	2	7		2	13	
Vomiting				3	20	

Notes: Related toxicities ≥ 3% incidence overall. Non-related grade 4 toxicities were reported.

Table 7: Patients Requiring Treatment Rest or Discontinuation Due to Related Joint Effects

	Treatment Rest		Treatment Discontinuation		Total	
	No.	%	No.	%	No.	%
5 mg BID (n=29)	5	17	3	10	8	28
25 mg BID (n=15)	3	20	3	20	5a	33

^aOne patient is counted in both the Treatment Rest and Treatment Discontinuation columns.

- In addition, 1 patient in the 5 mg dose group discontinued prinomastat after less than 2 wks of treatment due to related nausea, reflux, and body aches.

Conclusions

Efficacy

- SD was observed in 9/29 patients (31%) receiving 5 mg prinomastat BID, with 7 patients experiencing stable disease for at least 16 wks.
- Two of these patients were stable ≥ 24 wks. One patient (1/15, 7%) treated with 25 mg prinomastat BID had documented stable disease at wk 8.
- The difference in stabilization of disease observed between the treatment arms is not considered significant. The sample size is too small to make clinically relevant comparisons. In addition, progression-free survival is similar between the treatment arms (approximately 8 wks).

Biomarkers/Pharmacokinetics

- Baseline values of plasma VEGF and urinary markers N-telopeptide, deoxypyridinoline and pyridinoline were significantly different in SD versus PD patients at wk 8 ($P < 0.05$). Additionally, patients with SD had sustained lower values of these markers during the study compared to PD patients. These findings, which are consistent with the literature, suggest that these markers may have prognostic value.
- The change in plasma TIMP-1 concentration at wk 8 from baseline was significantly lower in SD versus PD patients.
- Although levels of many markers were lower over the course of the study in SD vs PD patients (eg, HER-2/neu), the differences were not statistically significant.
- Prinomastat PK were not different in SD versus PD patients.

Safety

- Reversible joint effects were the predominant toxicities. While both doses were well tolerated, the percentage of patients who experienced arthralgia and the percentage who discontinued treatment for joint effects was 2-fold higher among patients receiving high-dose prinomastat.

Future Directions

- Earlier stage disease may be a more appropriate disease setting for treatment with an MMP inhibitor.
- Prinomastat is currently undergoing phase II evaluation in other disease settings.

Acknowledgements

The authors gratefully acknowledge Jorge Escobar for biomarker sample analysis and management, Mark Knowles, PhD and Min Zhang for the statistical analyses, and Mario Napoli for the production of the data summaries and listings.

ABBT0556331

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GENERAL POSTER, SUN, 8:00 AM - 12:00 PM

Phase II Study of the Matrix Metalloproteinase Inhibitor Prinomastat in Patients with Progressive Breast Cancer. H. S. Rugo, D. Budman, C. Vogel, S. Baidas, G. Fleming, M. Collier, M. Dixon, Y. Pithavala, N. J. Clendeninn, D. Tripathy, D. Hayes; University of California San Francisco, San Francisco, CA; North Shore University Hospital, Manhasset, NY; Columbia Cancer Research Network, Plantation, FL; Lombardi Cancer Center, Georgetown University, Washington, DC; University of Chicago, Chicago, IL; Agouron Pharmaceuticals Inc, A Pfizer Company, La Jolla, CA

Matrix metalloproteinases (MMPs) are enzymes that degrade the extracellular matrix. Prinomastat (AG3340) is a potent MMP inhibitor designed using X-ray crystallography that reduced tumor angiogenesis, invasion, and metastasis in preclinical models. Patients (pts) having metastatic breast cancer that progressed on most recent therapy were randomized to 5 or 25 mg prinomastat administered orally twice daily. The rate of stable disease (SD), time-to-progression (TTP), potential biomarkers of MMP inhibition and the safety of single agent prinomastat were studied. 15 pts were to enroll into each treatment arm with expansion to 30 pts in an arm if at least one pt had SD at 8 weeks. A total of 44 female pts were enrolled, 29 pts received 5 mg and 15 pts received 25 mg prinomastat. Median age was 58 years (range 37-84), 93% of pts had failed chemotherapy in the metastatic setting, 55% had visceral metastases, and 70% had measurable disease. Musculoskeletal effects (hypothesized to be related to MMP inhibition) required treatment rest or discontinuation in 21% of pts at 5 mg between weeks 8-24 and 27% of pts at 25 mg between weeks 4-8. No objective disease responses were observed. Median TTP was 8 weeks in both arms, 9/29 pts in the 5 mg dose arm had SD at week 8, with 5 pts stable for at least 16 weeks. Preliminary analyses indicate that some biomarkers had potential prognostic value or paralleled disease progression. Low pretreatment plasma VEGF (<40pg/mL) and urine pyridinoline levels (<90pmol/ μ mol creatinine) correlated with SD at 8 weeks [67% vs 25% ($p<0.05$), and 100% vs 42% ($p<0.005$) for SD vs PD at week 8, respectively]. Further analyses of disease stabilization and correlative studies will be presented.

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GENERAL POSTER, SUN, 8:00 AM - 12:00 PM

Survival Benefit of Trastuzumab (Herceptin) and Chemotherapy in Older (Age > 60) Patients. G. A. Fyfe, R. Mass, M. Murphy, D. Slamon; Genentech, Inc, South San Francisco, CA; University of California-Los Angeles, Los Angeles, CA

The pivotal trial of Herceptin (H) plus chemotherapy (C) (doxorubicin/epirubicin and cyclophosphamide (AC) or paclitaxel (T) versus C alone in first-line therapy of metastatic breast cancer (MBC) demonstrated improved responses rate (RR) (50% versus 38%, $p=0.003$) and improved survival (S) (odds ratio, 0.80, $p=0.053$). This survival benefit was observed despite a design that resulted in 65% of control patients to receive H at disease progression. Eligibility for this trial was not restricted by age. We are reporting a retrospective exploratory analysis to determine the influence of age on clinical benefit from H in this trial. A total of 469 patients were enrolled; 360 (77%) age ≤ 60 and 109 (23%) age 60. Baseline characteristics were similar between the 2 groups with the following exceptions: age 60; worse baseline KPS (41% vs. 30% ≤ 80), higher initial nodal burden (≥ 4 , 52% versus 34%) longer disease-free interval from adjuvant therapy (26 versus 20 mo.), more frequent prior exposure to hormonal therapy (71% vs. 54%), and less frequent adjuvant exposure to anthracyclines (31% vs. 40%). In the age ≤ 60 group, the addition of H to C improved RR from 33% to 52% and S from 23 to 26 mo. In the 60 group the addition of H to C improved RR from 28% to 44% and S from 14 to 19 mo. Cardiac dysfunction (CD) in the H + T arms occurred in 11% of the ≤ 60 group and 21% of the 60 group. All CD events in the 60 group improved to grade 1 and H was continued. Conclusions: The group of HER2+, age 60 appeared to have a worse overall outcome compared to the ≤ 60 group, possibly related to adverse baseline characteristics. However, the survival benefit in the age 60 group from the addition of H to C was significant (relative risk 0.64 95% CI: 0.41-0.99). These data suggest that older (age 60) patients with MBC should be considered for first-line H + C therapy.

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GENERAL POSTER, SUN, 8:00 AM - 12:00 PM

Phase II Trial of a Doxorubicin, Docetaxel, and Cyclophosphamide Triplet (ATC) for Locally Advanced and Metastatic Breast Cancer: Preliminary Results from NSABP B-58. R. E. Smith, S. Anderson, B. Lembersky, N. Dimitrov, S. Desai, C. Kardinal, E. Marmounas; NSABP Operations and Biostatistics Center, Pittsburgh, PA

Based on the recommended Phase II doses for AT (doxorubicin (A: 60 mg/m²) plus docetaxel (T: 60 mg/m²) and the NSABP's experience with A plus C (Cyclophosphamide 600 mg/m²) (AC), we conducted a Phase II trial at 18 institutions using ATC q 21 days, in preparation for a major adjuvant breast cancer (BC) study (NSABP B-30) in which ATC would be used. Eligibility requirements included measurable stage IIIB/IV BC, performance status 0-2, normal LVEF, no prior chemo (except non-taxane adjuvant chemo, if completed > 12 months before entry) and cumulative A [symbol:Symbol (PCL6)/163]240 mg/m². Eighty-nine patients were entered: age range, 30-78 yrs (38.2% < 50 yr; 61.8% [symbol:Symbol (PCL6)/179]50 yrs); 33.7% with stage IIIB, 66.3% with stage IV BC; 20.3% stage IV pts, received prior adjuvant chemo. Dexamethasone premedication (8 mg po bid X 3 doses) and prophylactic ciprofloxacin (500 mg po bid days 5-15) were used. Growth factors (GF) were reserved for secondary prophylaxis after prolonged or febrile neutropenia (FN). When cumulative A = 480 mg/m², pts could continue with TC alone. Results: 88 pts and 536 courses were evaluable for toxicity. Median time on study was 17.5 months (range = 9-28). FN occurred in 33 pts (37%); 10 had FN in the absence of GF support; 23 had FN despite GF support. There were no septic deaths. 1 pt died from pulmonary embolism. Other grade 3-4 adverse events included: nausea 9%, vomiting 7%, stomatitis 6%, diarrhea 4%, arthralgia/myalgia 3%, neurocortical 1%. Clinical CHF was seen in 4 pts (4%). To date, 58 pts are evaluable for best response: there has been CR in 5 pts (5.6%); PR in 39 pts (43.8%); SD in 9 (10%). Conclusions: ATC with primary ciprofloxacin and secondary GF prophylaxis is well tolerated and active. Its value in the adjuvant setting is currently under investigation. Presentation will include updates. (Supported by PHS grant U10CA12027 and Aventis Pharmaceuticals)

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GENERAL POSTER, SUN, 8:00 AM - 12:00 PM

A Randomized Phase II Study of Alternating (AA) vs Sequential (SS) vs the Combination (CC) of Doxorubicin (A) and Docetaxel (T) as 1st Line CT in MBC. P. S. Cresta, G. Grasselli, A. Martoni, G. Lelli, M. Mansutti, G. Capri, F. Buzzi, G. Robustelli, L. Frevola, S. Mekhaldi, N. Azli, L. Gianni; Istituto dei Tumori, Milan, Italy; Ospedale S. Orsola Malpighi, Bologna, Italy; Ospedale Casa Sollievo della Sofferenza, San Giovanni Rotondo, Italy; Ospedale San Maria della Misericordia, Udine, Italy; Ospedale Civile Santa Maria, Terni, Italy; Istituto di Ricovero e Cura a Carattere Scientifico, Pavia, Italy; Aventis Pharma S.A., Lainate, Italy

Schedule of administration may affect the therapeutic results of active drugs. To test the optimal way of administering A and T in breast cancer patients, we performed a randomized trial comparing alternating administration (AA) of three-weekly A (75 mg/m²) plus T (100 mg/m²) for 8 overall cycles, vs. sequential (SS) A (4 cycles) followed by T (4 cycles) at the same doses, vs. combined (CC) A and T at 60 mg/m² each (8 cycles). From 11/96 to 01/00, 121 MBC patients were treated (AA=42; SS=38; CC=41). Patient characteristics were well balanced between arms: median age was 53 yrs (24-69), WHO PS 0 (0-1). Fifty-three patients (44%) had prior chemotherapy (16 prior anthracyclines) as adjuvant. Tumor involved 2 sites in 52, 45 and 32% of patients (arms AA, SS and CC, respectively). Visceral involvement was present in 74, 84 and 66%, and liver involvement in 46, 42, 46%. Median cycles was 8, median relative dose intensity higher than 0.9 for each drug in each arm. Febrile neutropenia (7, 0, 22%), grade 3/4 infections (0, 0, 2%), and grade 3/4 stomatitis (5, 5, 12%) were higher in arm CC. At median 22 months of follow-up, four episodes of congestive heart failure occurred in arm CC (10%) at cumulative A dose of 480 mg/m². The overall response rate was similar in all arms (57, 67 and 66% respectively). Time to progression was 34, 33 and 36 weeks, respectively. Analysis of survival is too early. In conclusion, all schedules of A and T were feasible and active as first line treatment for MBC. The combination regimen was more toxic, and the higher cumulative dose of A in that arm explains the observed cardiac toxicity. Survival data and further Phase III investigations will clarify the respective merits of the different schedules.

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ORAL PRESENTATION, TUE, 9:45 AM - 11:45 AM

Interim Results of a Phase III Study of the Matrix Metalloproteinase Inhibitor Prinomastat in Patients Having Metastatic, Hormone Refractory Prostate Cancer (HRPC). F. R. Ahmann, F. Saad, R. Mercier, R. A. Huddart, J. T. Roberts, M. Collier, L. Belletcourt, M. H. Zhang, N. J. Clendeninn, G. Wilding, Arizona Cancer Center, Tucson, AZ; CHUM-Nortre Dame, Montreal, Canada; Marshfield Clinic, Marshfield, WI; The Royal Marsden, Sutton, UK; Newcastle General Hospital, Newcastle, UK; Agouron Pharmaceuticals Inc., A Pfizer Company, La Jolla, CA; University of Wisconsin, Madison, WI

Matrix metalloproteinases (MMPs) degrade extracellular proteins, facilitating tumor invasion, angiogenesis, and metastasis. Prinomastat (AG3340) is a potent inhibitor of MMPs that demonstrated efficacy in preclinical in vivo tumor models. A phase III trial investigated prinomastat in combination with mitoxantrone (M) and prednisone (P) in chemotherapy naive patients (pts) having metastatic HRPC. M was administered intravenously at 12 mg/m² q3weeks and P orally, 5mg twice daily. Pts were randomized to 5 or 10mg prinomastat or placebo, orally twice daily. Between 4/98 and 7/00, 553 pts were enrolled; interim results are available for 406 pts. Baseline characteristics were balanced with median age 71 years, median PSA 94 ng/mL and 33% measurable disease. M+P dose-intensity and toxicity were comparable among the treatment arms. Musculoskeletal effects (MS, hypothesized to be related to MMP inhibition) were the only adverse experiences having time- and dose-relationship to prinomastat. Symptoms included arthralgia, joint stiffness and swelling and, rarely, tendinous contracture. Grade-2 MS were observed in 13, 22 and 22% of pts in the placebo, 5 and 10mg arms, respectively; events persisting for at least 3 weeks were managed by treatment-rest and prinomastat dose reduction. No differences were observed among the treatment arms in PSA response rate (RR, 75% reduction for 3wks); progression-free survival by radiography (RPFS, 50% increase for 3wks), or symptoms (SPFS); or overall (OS) and 1-year survival. Efficacy was not enhanced by the addition of prinomastat to M+P in pts having metastatic HRPC.

Efficacy Parameters

	Patients	PSA/RR	Median (months)			1-Year Survival
	Randomized	(%)	RPFS	PSA/PFS	SPFS	OS (%)
M+P-Placebo	138	14	6.0	6.8	7.7	14.8
M+P-5mg	134	17	6.0	8.9	8.6	15.1
M+P-10mg	134	18	4.7	6.5	8.3	14.7

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ORAL PRESENTATION, TUE, 9:45 AM - 11:45 AM

The Endothelin-A Receptor Antagonist Atrasentan (ABT-627) Delays Clinical Progression in Hormone Refractory Prostate Cancer: a Multinational, Randomized, Double-Blind, Placebo-Controlled Trial. M. A. Carducci, J. B. Nelson, R. J. Padley, T. Janus, R. Hippensteel; Johns Hopkins University, Baltimore, MD; University of Pittsburgh, Pittsburgh, PA; Abbott Laboratories, Abbott Park, IL

In hormone refractory prostate cancer (HRPCa), death is typically preceded by painful, osteoblastic skeletal metastases. Pre-clinical studies indicate that endothelin-1, via the endothelin-A receptor, inhibits apoptosis, stimulates proliferation of prostate cancer cells and osteoblasts, and is nociceptive. We evaluated atrasentan, a highly-potent (K_i=34 pM), selective (1800-fold), orally bioavailable, endothelin-A receptor antagonist as a treatment for men with HRPCa. Castrate patients, with adequate anti-androgen withdrawal, were randomized to placebo (n=104), 2.5mg atrasentan (n=95) or 10mg atrasentan (n=89) once daily. 244 patients were evaluable for the primary endpoint of time to clinical progression, defined as a disease-related event requiring intervention, disease-related pain requiring opiate therapy, or new lesions on imaging studies. Secondary endpoints included time to PSA progression, biochemical measures of metastatic progression and quality of life. Atrasentan patients had a statistically significant delay in time to clinical progression (2.5mg, 10mg) and PSA progression (10mg) compared to placebo. Atrasentan attenuated markers of metastatic progression including acid phosphatase, LDH, and alkaline phosphatase (p<0.05). The most common treatment-related adverse events (10mg vs. placebo) included peripheral edema (35% vs 14%), rhinitis (28% vs 13%), and headache (20% vs 10%), which were mild to moderate in nature and resulted in few discontinuations. No differences in treatment-emergent grade 3/4 toxicities were observed. Atrasentan sustained a favorable health status for a greater duration as determined by performance status and measurement of quality of life. Atrasentan represents a new, well-tolerated, oral, cytostatic therapeutic paradigm for men with HRPCa.

	Placebo	2.5mg Atrasentan	10mg Atrasentan
Median Time to Clinical Progression	129 days	184 days*	196 days*
Median Time to PSA Progression	71 days	134 days	155 days*

*Log-Rank test vs Placebo (p<0.05)

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ORAL PRESENTATION, TUE, 9:45 AM - 11:45 AM

Preliminary Evidence That Oral Clodronate Delays Symptomatic Progression of Bone Metastases from Prostate Cancer: First Results of the MRC Pro5 Trial. D. P. Dearnaley, M. R. Sydes, on behalf of the MRC PRO5 collaborators; The Institute of Cancer Research and Royal Marsden NHS Trust, Sutton, UK; MRC Clinical Trials Unit, London, UK

BACKGROUND: Bone is the most common site of metastases from prostate cancer (PCa). Bisphosphonates have been shown to slow development of metastases from breast cancer and myeloma and to modify bone pain in skeletal metastases from PCa. **DESIGN:** Phase III double-blind placebo-controlled randomised controlled trial of oral bisphosphonate in men commencing or responding to standard hormonal treatment. **Primary endpoint:** time to development of symptomatic bone progression or PCa death. **TREATMENT:** Either (A) 4 tablets/day (2,080mg) of oral sodium clodronate (Loron 520) or (C) 4 tablets/day of matching placebo. Patients (pts) were encouraged to stay on trial medication for 3 yrs or until the primary trial endpoint had been reached. **RESULTS:** Patients: 311 pts were randomised over 4yrs (6/94-7/98): 156A, 155C. Baseline characteristics were well balanced. Median follow-up to date is 3 years. Medication & Toxicity: Median time on trial medication was 18 months(m) for A (95%CI 15-21) and 16m (95%CI 12-20) for C. 259 patients have stopped trial medication, 29 (13A, 16C) after 3 years of treatment, 155 (65A, 90C) after symptomatic bone progression and 75 (48A, 27C) because of Adverse Events (AEs) or pt preference. AEs were reported more often for A (118AEs/75pts vs 69AEs/48pts, Relative Risk=1.79, p=0.0014) & required modification of trial medication dose more often (52 vs 20 pts, p=0.0001). Gastro-intestinal problems and raised LDH were the most common adverse events. **Primary Endpoint:** 202 patients have reached primary trial endpoint, 93 A and 108 C; Hazard Ratio (HR)=0.75 (95%CI 0.57-0.99) in favour of A (p=0.044). At 2yrs, 51% (95%CI 44-59) A and 41% (95%CI 33-49) C had not reached primary endpoint. Median time to primary endpoint is 26m (95%CI 21-31) for A and 20m (95%CI 16-23) for C. Survival: 82 A and 94 C patients have died; HR=0.80 (95%CI 0.59-1.07) in favour of A (p=0.13). At 2yrs survival is 66% for A and 59% for C. Median survival is 34m for A and 27m for C. **COMMENTS:** These preliminary results provide evidence that oral sodium clodronate delays progression to symptoms from bone metastases in PCa. Updated results will be presented at the meeting.

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ORAL PRESENTATION, TUE, 9:45 AM - 11:45 AM

A Prospective Randomized Trial of Antiandrogen Withdrawal Alone or Antiandrogen Withdrawal in Combination with High-Dose Ketoconazole in Androgen Independent Prostate Cancer Patients: Results of CALGB 9583. E. J. Small, S. Halabi, J. Picus, N. Dawson, Y. Chen, N. J. Vogelzang; University of California, San Francisco, San Francisco, CA; Duke University, Durham, NC; Washington University, St. Louis, MO; University of MD, Baltimore, MD; University of Chicago, Chicago, IL

High-dose ketoconazole (HDK) has been shown in several phase II trials to reduce PSA levels in approximately 50% of androgen-independent prostate cancer (AiPCa) patients, with variable durations of response reported. CALGB 9583 sought to compare the response proportion and duration of response to antiandrogen withdrawal (AAWD) alone versus AAWD combined with HDK. "PSA response" was defined per consensus criteria. 261 AiPCa patients were randomized to AAWD alone (N = 132), followed by "crossover" to HDK at progression or to AAWD plus simultaneous HDK (N = 128). Ketoconazole, 400 mg p.o. t.i.d., was dosed with hydrocortisone, 40 mg p.o. q.d. Results are summarized below. These data suggest that the "PSA response" to AAWD in a large multicenter prospective cohort is modest, at 13%. Response to AAWD + HDK was higher (27%), but still lower than previously reported. There was no difference in survival in ear versus later use of HDK, and overall toxicity was modest.

	AAWD alone (n = 132)	AAWD + HDK (n = 128)	P value
PSA response	13%	27%	0.012
Objective response	4%	13%	0.016
Survival (incl. crossover pts)	16 mos.	15 mos.	0.792
Grade 3/4 toxicity	4%	22%	0.002

5-12-01

American Society of Clinical Oncology - SF

#342 → triketone ~ could not detect Δ's w/ histone acetylation w/ PM cells ~ perhaps technical difficulty

#345/6 → CI-994 "cytostatic" agent ~ pursuing w/ combination (not effective alone)

#344 → more toxic^{w/ SAHA} in hematological patients (but could be that they are more sick)

- don't know selectivity profile
- preclinical models suggest transient HDAC inhibition is cell first is necessary ~ will probe this clinically. (difference in doing protocols is being used to assess this)

#395 - BMS245291

- safe & well tolerated
- linear PK; steady state by day 7
- no joint effects different than placebo!
- no adverse ~~events~~ ^{lack of} w/ PK normal/patient
- they think it's ^{lack of} ~~glucose~~ vs. ~~glucose~~ / hydro
- will continue in combination therapy!

#311 → TAC + PhBu ~ specifically excluded HIV infected patients from trial ~ like
Chas thought about idea of latent virus activation followed by anti viral therapy,

#387 → BMS 275291 ~ no DLT no joint effects
BID oral dosing OK
mean PK

Nabulsi Deposition Exhibit 27

D's Exhibit LF– Part 13

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phase II dose 1,200mg/d No effect on TNF levels
 - dermal wound angiogenesis delayed by treatment

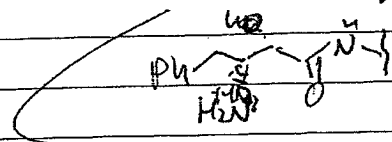
some grade 1 myalgia/arthralgia but not dose dependent. } not dose limiting

Kato, H - Phase Phase III: Ubroxime (bestatin)

inhibits aminopeptidase N

" B

leucine aminopeptidase



phase III Low NSCLC

→ some benefit in overall survival (significant)

2 year survival better & significant difference
 placebo

potentially mediated by anti angiogenic effect?

Squamous cell carcinoma of the lung?
 adenocarcinoma of the lung?

For
 squamous
 cell
 carcinoma
 of the
 lung.

+ Smylie Phase III NSCLC

A33402 (me/cisplatin) +/- pimonidazole

5, 10, 15 BID + PC 686 patients - (chemo naive)
 - Stage III B

no difference in any dose

in terms of overall survival & progression-free survival

symptomatic PFS (no difference)

grade 2 tox - dose dependent at higher

no benefit / no detriment

253

done ~~last~~ to x @ higher dose

^{1-year}
trend to better survival, but not significant

+ comparison of bestatin vs pirostat

~~post-operative~~ given ~~post-op~~
surgery

advanced stage
patients

adjust chemotherapy

^{bestatin}
~~Observation~~ → what is mechanism? why just squamous cell?

+301 BMS-275291

S, S, S

→ natural sterosteroid converted to 20-~~old~~
less active R, S, S. QD

→ will go into NSCLC / Pax-Carbo phase II
Kaposi Sarcoma "

→ ~~phase~~ would healing assay showed
delay, but dose dependency ~~is~~ not strong.

+302 → Col-3 — reduction in MMP2 & 9 expression
w/ Col-3, but not dose related

∴ → still relying on PK data to drive
phase III dose.

5-13-01 +187 Pirostatat PK

→ pursuing another disease settings

phase II trials in earlier stage disease (to
cancer — but wouldn't say what)

→ will read these results as a gap/no go.

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+ Kerkel (Toronto) Angiogenesis Inhibitors / Endothelial ADR

growth of solid tumors beyond 1-2 mm requires angiogenesis.
Folkman NEJM 285 1991

sex hormones (estrogen, androgen) ~~are~~ ^{are} pro-angiogenic
endogenous

most anti-angiogenic factors are

- fragments of other proteins
- some are involved in coagulation cascade.

angiogenesis

- receptor tyrosine kinases (VEGF)
- integrins
- proteolytic enzymes (MMP)
- non proteolytic enzymes (MMP2)
- membrane glycoproteins

Vogelstein Science 2000 289 1197-1202 SAGE

genes expressed by the angiogenesis

angiogenesis 2 types

characterizing

←

↓

microphallid
infection

DNA

tags

isolation

anti-angiogenic → many targets.

many different targets

accidental anti-angiogenic

- thalidomide

- interferon

- signal transduction

J of Clinical Oncol 2001 - Sledge.

acquired resistance to anti-angiogenic can be a problem

1. reduction of target
2. upregulation
3. epigenetic
4. heterogeneity of GC to effects

255

www.angio.org meximune dosing

† Herbst (MD Anderson)

Endostatin... ~~early~~ phase I PK / surrogate markers.

↳ collagen fragment.

(tissue biopsies)

(non-invasive blood flow)

i.v. infusion over 20 minutes every day

no untoward effects

$t_{1/2} = 10$ hours linear AVE

but only
beats...
noting
significant.

most patients progressed as most phase I studies.

Some cases of ↓ blood flow; ↓ glucose metabolism.

Glucose PET

^{15}O PET

biopsies → looked @ EC apoptosis and @ CD31 (blood vessel).

→ will go with the continuous infusion

† Demeraz ^{isolated}

Folkman identified angiogenesis: angiostatin from blood of
angiostatic 15 ng/ m^2 → ^{24h} continuous infusion

↳ adverse events → grade 2 rash.

- no DLT; no effect on wound healing (as observed

- following surgery)

$t_{1/2} (X) = 20$ min $t_{1/2} (P) = 3$ hours

- higher doses cause antibody formation.

- PK is linear.

- no significant reduction in objective responses

→ "don't think they are neutralizing" no D in plasma level

how long it
can be
stable
in
pump?

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+ Shepherd (Canada)

marimastat in SCLC Following 1st line therapy Phase III
 randomized double blind

MMPE expression frequently elevated in SCLC

SCLC patients ... most respond to 1st line therapy, but
 most ~~progress~~ relapse shortly after.

555 540 patients

marimastat 10mg PO BID vs placebo up to 2 years or placebo

	marimastat	placebo	} no difference
PFS	4.32	4.44	
95% OS	9.4	9.7	

no differences in survival, even among patients w/
 early stage disease.

1/3 of patients on marimastat needed dose modification due to
 a musculoskeletal \pm effects.

marimastat \rightarrow poorer quality of life.

\pm trials continue in gastrointestinal cancer.

Would it work if you could higher? \rightarrow BMS will answer this

O'Reilly (MD Anderson)

CT scans

PET scans

Imaging of blood flow (15O) and metabolism (FDG) ^{Phase}
 of tumors using PET.

+ Nelson

Endothelin-A receptor antagonist - Abiraterone

in men w/ hormone refractory
 Prostate Cancer

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PC --- associated w/ bone metastases, pain.

--- can monitor disease progression by markers of bone remodeling.

- ET-1 ↑ w/ PA

- ET-A ↑ w/ PA

- osteoblast express ETAREceptor.

627 -10mg
 -2.5 } 12 weeks (paw)
 - placebo

QD po

PC patients → Δ w/ bone biochemical markers.

~ 2-4 fold ↑ of alkaline phosphatase etc.

--- these ↑ w/ disease progression.

--- dose dependent reduction in markers.

~ (10mg dose brings ↑ to baseline).

also did bone scans --- trend to reduction.

→ dose dependent ↓ in ~~size~~ of PSA.

shown to
drug does not effect PSA production itself.

+ Linderholm

high VEGF associated w/ ↓ survival

low bFGF

"

"

"

"

"

RFS + relapse

free survival

+ Jayson

Anti-VEGF antibody HuMV833

human monoclonal IgG4 anti-VEGF ab

large differences in rate of clearance of mAb from

tumor vs. normal tissues

→ (some high, some low)

reduction in tumor vascular permeability by ~~the~~ ^{correlates of stable} disease in some tumors.

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+ Sledge (Indiana University)

BT-1 → weakly mitogenic itself but enhances mitogenic activity of other growth factors

AD-627 → does not effect growth of tumors outside of bone

5-14-01 + Deborah Calkins - Breast Cancer Symposium
Liz Eisenhauer -

neoadjuvant? vs. post-operative

diagnosis — via biopsy

Staging — via chest X-ray
chemotherapy
bone scanmore
par-1's? enlightened
history
mus/in.

+ Fogler (Entrez)

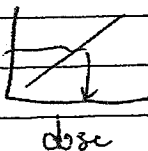
rh Endosteal PK

→ gives consistent & predictable PK

→ iv infusion of 20-60 minutes. ($15-600 \text{ mg/m}^2$)

cloned from pte yeast (picra)

1st patient treat in October 1999

PK analyzed by biotinylated endosteal competition assay
 $V_d = 350 \text{ L/m}^2$??Ave 
dose

preclinical Ave — not necessary for efficacy suggests used to determine clinical dose

Phase II dose → 60 mg/m^2 (but infusion vs. bolus
is ~~under~~ underexplored
at this point).

Nabulsi Deposition Exhibit 27

D's Exhibit LF– Part 14

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→ Endostatin
 + Eder → Dana Farber Cancer Institute.
 → phase I pt. daily infusion over 20.7 months.
 only tox is rash. (some evidence of catheter-related sepsis)

markers → serum ~~as~~ EC antibodies
 → urinary VEGF / bFGF
 → circulating EC precursor cells.
 → # of KDR positive cells.

vasculogenesis? no evidence of efficacy.
 angiogenesis? (some stable "prolonged" periods of stable disease)

→ difficult to get patients to come to clinic every day for infusion
 → no data on dose dependency of circulating EC precursor cells.

+ Thomas (Univ of Wis.) Endostatin.

Phase I is it safe? is it there? is it working?
 - some Ab formation, but no allergic reaction.
 - trough levels consistent w/ preclinical efficacy.
 - some metabolism to shorter peptides.
 tumor glucose uptake (PET).

saw it in circulating VEGF, but not dose dependent.

It's no contrast enhancement by CT.
 is there a correlation between those patients w/ stable disease and effects on markers?

what to do to extend t_{1/2}? What is target?

+ Muddheke

EC knows no skin wounds a tumor of patients receiving endostatin

260

all end stage patients

21 patients

18 gauge needle biopsy

Skin wound assay (4mm punch biopsies)

2 tumor biopsies from each patient 0-8 weeks

- no Δ in microvessel density or for EC proliferation from tumor biopsies in tumor pre-treated vs. treated
- endostatin did not alter wound healing parameters, endostatin - no Δ in tumor vessels
- no Δ in wound healing

→ does assay work in animal models in which endostatin shrinks tumors? → no Δ in wound healing in these mice (From Folkman lab)

+ Galbraith

Combretastatin A4 phosphate (CA4P) ^{prodrug}

→ vascular targeting agent.

dynamic contrast enhanced MRI

→ infuse of paramagnetic Gd-DTPA

... visualization correlate w/ blood flow

→ CA4P shows reduction in tumor blood flow

if these
does not correlate,
then MRI

↓ in blood flow

by MRI is
a PD
marker,
not a

surrogate
marker.

- looked at various tissues

- saw dose dependent ↓ in tumor vs blood flow w/ CA4P whereas no such Δ in muscle, ... but toxicity seen @ higher doses.

68 mg/m² is MTD → significant ↓ in tumor blood flow @ this dose.
correlated

tumor size correlates w/ ↓ in blood flow in one patient but these tumors re. w/ therapy progress

What level of tumor ↓ in tumor blood flow correlates w/ ↓ in tumor size in preclinical studies,

261

+ Thomas PD results using dynamic contrast enhanced MRI of 2 phase studies of PTK787 = ZK 222584 in patients w/ liver metastases from colorectal cancer.

DCE-MRI \rightarrow measures blood flow & vascular permeability.

Study design - modified Fibonacci

doses $50 \rightarrow 1,500$ mg/day $t_{1/2}$ 4-5 hours.

- no accumulation

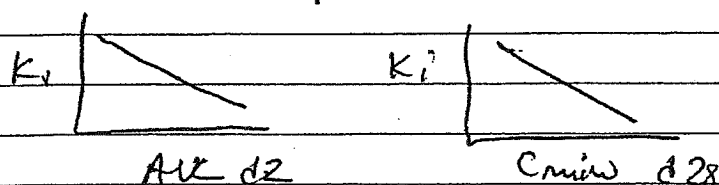
day PTK787

\rightarrow shows marked

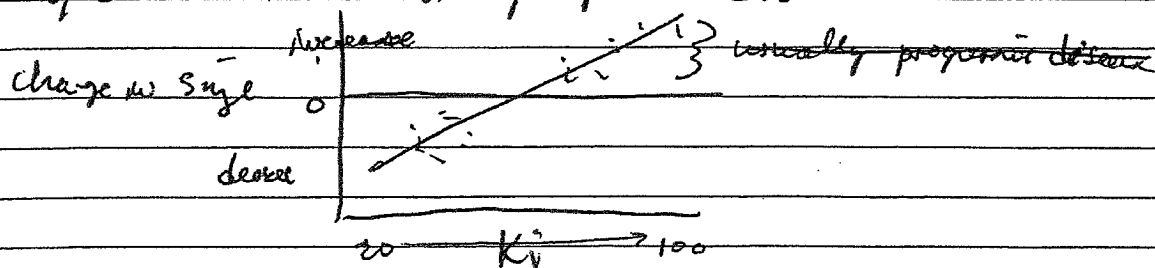
no flow in liver mets

\rightarrow dose-dependent reduction in K_i (flow)

- no Δ in t_{max} $t_{1/2}$ between day 1 & day 28



Δ in K_i higher reduction in K_i among patients w/ stable disease vs. progressive disease.



+ James Pluda (NCI) \rightarrow pig-mouse model
Function imaging PET O^{15} ; ^{11}CO ; ^{18}F -flugh

+ Pavg STI571 PK/PD relationships
phase I study

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CML \rightarrow associated w/ \uparrow WBC.

Bcr-Abl is present w/ Philly chromosome - positive cells

PK \rightarrow how much & how

PD \rightarrow investigate sensitive markers

PK/PD \rightarrow establish phase II dose

25 \rightarrow 750 mg/day PO; QD.

PD = plasma WBC

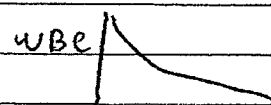
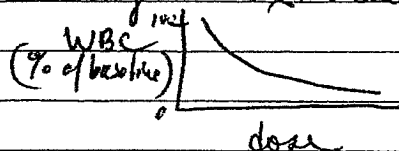
(1 μ M)

PK doses of 571 \geq 400 mg maintain [plasma] \geq 500 ng/mL

- no accumulation between day 1 & day 28
- linear PK

Significant reduction in WBC on over first month.

Inhibitory Emax model



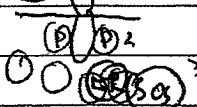
dose

log₁₀ (C_{max})

Ave

@ dose of 400 mg and up, all WBC go to normal range for ^{all} ~~path~~
 \rightarrow one major metabolite in plasma (active) - but only 6% of total AUC
 + Hidalgo OSI-774 EGFR inhibitor.

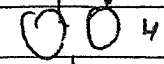
GP



\rightarrow now @ 100 mg/day
 assess EGFR cellular activity

used to validate method

phosphospecific antibodies used on biopsies



cell effects

cell ~~is~~ overexpression TGF- α TGF- α
 (add TGF- α , turn off TGF- α)

immunohistochemical methods

• Skin biopsy of patients ... showed blockade of EGFR activity w/ OSI 774 in a portion of patients (~30%)

• Tumor tissue \rightarrow some patients show evidence of EGFR blockade in tumor, better effects in patients w/ EGFR overexpression.

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were expecting that one would see ↓ w stem, ^{but why} ~~but why~~ no?
 → measured blockade of several pathways - ~~akt pathway~~
 is less OSI appears less active on akt pathway.

+ Bee Tressa (ZD1839) is effective inhibitor of tamoxifen-resistant breast cancer growth.

regrowth of breast cancer tissues is associated of ↑ EGFR expression

Cultured cells w presence of tamoxifen to produce resistant cells. → these cells ~~to~~ overexpressed EGFR

→ ~~from~~ - had ↑ Phospho ~~EGFR~~ EGFR

→ - - had ↑ Phospho MAPK (ERK1/2)

ERK1 & ERK2 are both MAPK

ZD1839 has no effect on growth of WT-MCF7 cells (non-EGF expressing), but significant inhibitory effect vs. tamox-resistant MCF7.

combination of tamoxifen + ZD1839 gives better ↓ w growth rate of cells MCF7 cells (∴ may be able to prevent development)

+ Barrison CT-1033

PK Phase I & PK of CT-1033

low ErbB tyrosinase
 given orally on day 1,
 8, & 15 every 28 days
 to patients w solid tumor.

rash;

GI problems

over-expression of erbB isoforms common in many tumors,
 CT-1033 hits erbB1, B2, B3, B4 (Tressa hits
 only B1)

100 mg/dose

measure ~~biopsy~~

biopsy, tumor marker & PK

1,000

grade

3 hypersensitivity (?)

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(antihistamine)

- needed to add oral desferrioxamine
- thrombocytopenia seen @ 750 + 1,000 mg

$V_d \rightarrow$ large; $t_{1/2} = 4.5$ hours.

Cmax & AUC were dose proportional
no accumulation

no relationship to plasma MB2 level!

no responses in some stable disease

MTD was 500 mg DLT = hypersensitivity reaction
to 750 \rightarrow thrombocytopenia.

+ Blumke STI571 in patients w/ GI tumors expressing C-kit
GIST (type of GI tumor)

\rightarrow no good therapy.

C-kit \rightarrow normal homologue of a viral oncogene
 \rightarrow implicated in various tumors.

C-kit mutation results in constitutively active
STI blocks C-kit mediated cell growth.

400 + 600 mg/day (24 months) 36 patients initially

\rightarrow 150 total.

C-kit detected by immunohistochemistry.

148

tumor response data PET, MRI; tumor biopsy.

^{18}F FDG-PET? \rightarrow anti-tumor activity

25% of patients required dose alteration due to drug.
GI bleeding, hepatotoxicity.

50% 58% of patients had partial response

26% stable

13% progression

265

↓ cellularity of tumor seen w/ ~~low~~ immunohistochemistry

86% of patients had c-kit mutation → these patients responded better.

"1st effective therapy for GIST" → fairly rare tumor
c-kit may predict response to ~~c-kit~~ STI-571

+ Oostrom. STI571 - phase I w GIST

most toxicities were non-hematological
(500mg bid - vomiting, nausea)
good absorption of drug despite GIST tumor.

most patients had some kind of response... only a few had progressive disease.

¹⁸FDFG PET-scan evaluation

CT scan versus PET scan.

right now, none of responders have relapsed.

"considerable" anti-tumor activity.

phase II SCLC; prostate cancer, glioma
recommended dose = 400mg bid.

conventional therapy 90% progression
STI571 11% "

it's not really
at heart we know
it's c-abl
mediated.

works well
works well w blast crisis w CML, but these patients ultimately relapse, since other factors effect of the proliferation. → in these relapse patients, Abi kinase activity is not blocked. due to ~~the~~ amplification of bcr-abl gene.

CML & GIST are rare, "single-hit" cancers
normal solid tumors are multiple hit just like

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but ... significant evidence that a single oncogene
plays a central role ~~in~~ even in a genetically
complex cancer (Do Prisco transgenic model).

w/ CML - need Bcr-Abl

w/ B1ST - need c-kit

9

Nabulsi Deposition Exhibit 29

D's Exhibit LG



ABBOTT

Pharmaceutical Products Division

Abbott Laboratories
Oncology Group
Dept. 048K/AP6A-1
100 Abbott Park Road
Abbott Park, Illinois 60064-6008

June 21, 2001

Dr. Jan Schellens
The Netherlands Cancer Institute
Plesmanlaan 121
1066 CS
Amsterdam, The Netherlands

Dear Dr. Schellens:

We wish to commend you for your efforts in helping us to bring forward the first study of ABT-518 in men and women. With your outstanding efforts we have learned much more about this compound.

Unfortunately, it has been decided to cease development of ABT-518 compound at this time. This decision was made after careful consideration of the clinical characterization of this class of compound and its business implications. Though the study is being terminated, patients currently on study may continue until the study endpoint has been reached. In addition, those patients who have already given informed consent to participate in the trial may be considered to receive drug.

We share your disappointment at this decision and want you to know that we remain strongly committed to the development of new therapies for patients with cancer. As we have previously discussed, Abbott Laboratories has a plethora of new drugs in discovery and we remain confident that many of these will be brought forward for clinical development. As these drugs become available for clinical study in men and women, please know that we will require your expertise and assistance in conducting future trials.

I regret we were unable to meet in person so I could communicate this information to you, but hope that we can meet in The Netherlands so I can discuss this decision with you and update you on future plans. Further communications regarding the logistics for discontinuation of study M00-235 will follow.

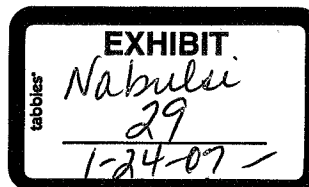
If you have any further questions please contact me or a M00-235 team member immediately.

Kind regards,

I remain,

A handwritten signature in cursive script, appearing to read 'Azmi A. Nabulsi'.

Azmi A. Nabulsi, M.D.



Nabulsi Deposition Exhibit 34

D's Exhibit LH

Pharmaceutical Products Division

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August 10, 2001

To: Perry Nisen D48J, AP30

Re: ABT-518

Below please find commentary on the results from the ABT-518 clinical trial, the status of the MMPi competition and an opinion on a path forward for Abbott's MMP inhibitor program. To summarize, the lack of clinical efficacy of competitors' compounds likely relates to their inability to maintain plasma concentrations above target levels, due to dose-limiting musculoskeletal effects. Based on the clinical data generated thus far, the exposure and toxicity profile of ABT-518 provides evidence that it may overcome these drawbacks. Completion of Phase I studies in cancer patients is recommended.

I. ABT-518 Clinical Results - Pharmacokinetics

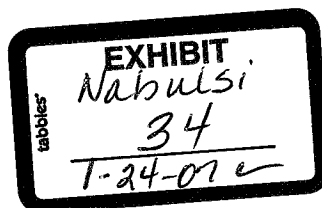
Despite the limited number of patients analyzed thus far, the pharmacokinetics produced by ABT-518 appears to have met our objectives. The estimated plasma half-life (20 hours) is consistent with once daily dosing and the C_{max}/C_{min} ratio (1.8 to 6) [1, 2] is far smaller than that produced by prinomastat (30 to 55).[3] The mean trough concentration for the two patients given a 50 mg dose of ABT-518 was 380 ng/mL (760 nM), a value within the range of our original target concentrations (see Section IV below). One concern based on preclinical animal studies was the possibility of ABT-518 inducing its own metabolism. While there is a trend towards lower AUCs on Day 22 versus Day 1, significant metabolic induction does not appear to be an issue for the 25 mg and 50 mg doses of ABT-518. It would be interesting to match ABT-518 exposure to patient gender, given the substantial differences that were observed in male and female rats preclinically.[4]

Based on the pharmacokinetic profile of one patient given a 25 mg dose over 22 days, metabolite exposure was low relative to parent drug, the highest metabolite to parent ratio being produced by the amine metabolite.[5] This is consistent with preclinical studies in rats and monkeys wherein "pharmacologic" doses of ABT-518 resulted in low metabolite to parent ratios.[6] It is important to recognize, however, that the analysis is not complete without assessment of the aryl sulfonic acid, a metabolite that was identified after development of the clinical assay.

II. ABT-518 Clinical Results - Toxicity Profile

The toxicity profile produced by ABT-518 is perhaps the single most important factor in deciding whether further development is justified. A summary of the SAEs observed during this study has been distributed however a determination as to whether these events were drug related is not yet available. Clearly, a decision on whether to propose additional studies with ABT-518 is contingent on these results.

Since abandoning the broad spectrum MMP inhibitor approach in 1997, we have argued that Abbott's gelatinase-selective MMP inhibitors would differentiate themselves from the competition by avoiding the joint toxicity "ceiling" seen with marimastat and prinomastat. Joint pain and tenderness was observed in approximately 33% of patients treated with a 10 mg dose of marimastat twice daily over 5 months.[7] Musculoskeletal effects significant enough to cause dose modification or discontinuation of treatment was



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seen in 27% of patients given a 25 mg dose of prinomastat twice daily over a 4 to 8 week period.[3] It is therefore quite encouraging that arthralgia & myalgia was not reported (as far we know) in any of the patients dosed with ABT-518 for as long as two months. While the number of patients is clearly too small to draw definitive conclusions, the lack of joint effects seen with ABT-518 is certainly suggestive that ABT-518 may indeed avoid the pitfalls of marimastat and prinomastat.

III. Competition

Since it appears that the development of ABT-518 is largely predicated on the status of competitors' compounds, a review of the latest news on the leading inhibitors is provided below.

Marimastat

2001 ASCO abstracts:[8, 9]

- Marimastat (10 mg, po, bid) did not enhance overall survival or progression free survival of SCLC patients following first-line therapy. A slightly smaller study involving patients with glioblastoma multiforme produced the same result.
- In the SCLC trial, a significant percentage of the patients required either dose modification (20%) or withdrew from treatment (18%) due to musculoskeletal effects.

Independent of the negative results reported for marimastat at the 2001 ASCO meeting its development status is a bit cryptic. The IDdb investigational drugs database indicates that one study of marimastat in patients with resected pancreatic cancer is being continued since interim analysis did not meet the stopping criteria. Surprisingly, little information is available on the follow-up to study 145 involving marimastat in gastric cancer patients. One report mentioned that "long-term data (from study 145) demonstrated that patients treated with marimastat continue to show survival benefit compared with those receiving placebo", yet this study does not show up on the BBT website nor can it be found in clinical trial databases.[10] To complicate matters further, the latest issue of the *Journal of Clinical Oncology* includes a paper indicating that marimastat is as effective as gemcitabine in treating patients with unresectable pancreatic cancer, but is associated with a lower incidence of grade 3 & 4 toxicities.[11] According to BBT executives, the future direction of marimastat development is the "subject of ongoing discussion with Schering-Plough and with external experts".[10]

Prinomastat

2001 ACSO abstracts:[3, 12, 13]

- Phase III studies of prinomastat (in combination with paclitaxel and carboplatin) in NSCLC patients revealed no benefit in terms of overall survival; this was also true for a Phase III combination study in patients with metastatic hormone refractory prostate cancer.
- In a Phase II study of prinomastat in patients with progressive breast cancer, joint toxicity required treatment rest or discontinuation in 21% of patients given a 5 mg dose between 8 and 24 weeks and 27% of patients given a 25 mg dose between weeks 4 and 8.
- When asked what the future holds for prinomastat, *each* of the presenters responded with "assessment in earlier stage disease", yet *none* of the presenters were willing to define the nature of these trials; a go/no go decision on prinomastat will be made following these studies.

Pfizer discontinued the Phase III studies mentioned above in August of 2000 due to failure to meet primary efficacy objectives. However, patients having earlier stage disease in a second ongoing NSCLC trial are

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apparently continuing treatment. The IDdb database indicates that prinomastat is being assessed in four Phase II trials with two additional trials planned.[14] The design of these trials and whether they are all being conducted is not known.

BMS 275291

2001 ASCO abstracts:[15 – 17]

- Phase I studies of BMS 275291 in healthy volunteers and cancer patients indicated that it produces no joint effects different than placebo; BMS scientists continue to believe that this reflects the compound's lack of sheddase activity.
- Due to the presence of the free sulfhydryl group, BMS 275291 forms disulfides with other thiol-containing compounds. Pharmacokinetic analysis of BMS 275291 therefore includes "free" (unchanged parent) and "total" (parent measured after disulfide reduction). Unchanged parent is believed to be the pharmacologically active form.
- The stereocenter adjacent to the thiol group of BMS 275291 is partially racemized to the 60-fold less active (R,S,S) diastereomer in humans. This is apparently a recent finding and may explain why some of the trough concentrations reported in the ASCO abstract differ from those presented at the meeting (see, for example, abstract #301 (Gupta, E. et al.): trough concentrations produced by the 1,200 mg dose at steady-state: abstract = 398-567 ng/mL; poster = 158 ng/mL).
- While C_{max} and AUC values of unchanged BMS 275291 increased in relation to dose from 600 to 1,800 mg, abstract #301 reports "no further increase in exposure between the 1,800 and 2,400 mg dose".
- The Phase II/III recommended dose is 1,200 mg, once daily. This dose produces unchanged parent trough concentrations of 158 ng/mL (Gupta study) which exceeds the gelatinase A/B IC₅₀'s for BMS 275291 (20 and 14 ng/mL), but exceeds the IC₅₀ value only for gelatinase B (gelatinase A IC₅₀: 261 ng/mL; gelatinase B IC₅₀: 119 ng/mL).
- Dermal wound angiogenesis (measured following punch biopsy) was delayed in patients treated with BMS 275291, yet this response was not dose-dependent, consequently their Phase II/III dose (1,200 mg) was chosen based on plasma exposure.
- Phase II studies include NSCLC patients in combination with paclitaxel/carboplatin as well as Kaposi's sarcoma patients.

The BMS data presented thus far suggests that inhibition of MMP1 does not mediate joint toxicity. Whether TACE is the culprit is not known; it remains possible that MMPI-induced joint effects are due to inhibition of some unknown metalloproteinase. Regardless, several observations suggest that BMS 275291 may have more ills than originally thought. First, there are no published reports describing its preclinical efficacy in cancer animal models. Given that the compound has been described at a number of major meetings, this may indicate that its efficacy in animal models doesn't compare favorably to the other MMP inhibitors being developed. BMS 275291 is not highly protein bound (ca. 60%),[15] yet its pharmacokinetics are confounded by disulfide formation as well as racemization to a less active diastereomer. While the lack of joint effects clearly provides BMS 275291 with an advantage over marimastat & prinomastat, the report that doses higher than 1,800 mg did not cause an increase in plasma concentrations suggests that this compound may also suffer from a dose "ceiling", albeit for reasons different than its predecessors.[15]

BAY 12-9566

2001 ASCO abstracts:[18]

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- Follow-up to study of BAY 12-9566 in patients with ovarian cancer which was closed (based on data from pancreatic/SCLC patients) after enrolling 243 patients. Results from this study indicate that BAY 12-9566 (800 mg, po, bid) was neither beneficial nor detrimental. This provides evidence that MMP inhibition is not inherently harmful to cancer patients.

RS-130830

Roche's "selective" hydroxamate-bearing MMP inhibitor (RS-130830) was apparently discontinued due to musculoskeletal side effects.[19] It's MMP inhibition profile is similar to ABT-518, although TACE data for RS-130830 has not been reported.

IV. Why They Failed & Why We Might Not

A commonly cited explanation for the failure of marimastat, prinomastat and BAY 12-9566 in Phase III clinical studies has been the idea that MMPs do not play a significant role in mediating the progression of advanced stage solid tumors. Results from the Phase II studies being conducted with prinomastat in earlier stage disease will hopefully shed light on whether this is indeed the case. Given the likelihood that objective responses will not be observed in these studies, the establishment of a pharmacodynamic marker of MMP inhibition is very important for our MMPI development program (see Section V). Measurement of MMP proteolytic activity in human tumors would also be useful in identifying tumors types likely to respond to MMP inhibitors. To date the choice of which tumors to target for Phase III trials has been based largely on MMP expression, a read-out that is only an indirect measure of MMP function. This is a consequence of MMP proteolytic activity being regulated at several post-transcriptional steps including proenzyme activation and endogenous inhibitor (TIMP) complexation.

Independent of whether MMP inhibitors will perform better in earlier versus later stage cancers, there is evidence to suggest that marimastat, prinomastat and even BMS 275291 are inappropriate tools to answer this question in the clinic. Figure 1 illustrates why. This figure provides a comparison of target plasma trough concentrations based on preclinical efficacy studies, with trough concentrations achieved in cancer patients (you'll recall that this analysis was presented at the March 2000 DDC meeting and again at more than one MMPI Transition Team meeting). Based on our own studies and those in the MMPI literature, continuous exposure to MMP inhibitors is necessary for maximal efficacy in cancer animal models, thus the emphasis on maximizing *trough* concentrations. We have argued that the gelatinases are the most important MMPs for mediating tumor progression, consequently the mean IC_{50} value for gelatinase A and gelatinase B is used in Figure 1 (using either value alone produces that same conclusion). Taking prinomastat as an example, its "plasma binding-corrected" (PBCed) IC_{50} value in mouse plasma can be determined by multiplying its mean gel A/B IC_{50} value (0.048 nM) by a factor representing its "free fraction" which is based on its mouse plasma protein binding value determined *in vitro*. Prinomastat's protein binding in mouse plasma was determined to be 81.6% (0.816) therefore its free fraction is 0.184 (1 minus 0.816) and its PBCed gel A/B IC_{50} value in mouse plasma is 0.26 nM (1 divided by 0.184 times 0.048 nM). To determine the trough plasma concentration of prinomastat associated with preclinical efficacy, it was administered by osmotic minipumps in the B16 subcutaneous tumor growth model. Efficacy was observed at a continuous (trough) plasma concentration of 57 nM. For prinomastat there is therefore a 218-fold shift between the mouse PBCed gel A/B IC_{50} value and the plasma concentration associated with preclinical efficacy.

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Prinomastat's mean gel A/B IC_{50} value can be corrected for binding to human plasma in either of two ways, mathematically from its *in vitro* binding to human plasma (analogous to the calculations above) or from the fold-shift in gelatinase A potency determined in the absence/presence of 80% human plasma. By either measure, the PBCed gel A/B IC_{50} value for prinomastat in human plasma (0.22 nM or 0.17 nM) is not too dissimilar from its value determined for mouse plasma (0.26 nM). Applying the 218-fold shift from above to this human PBCed gel A/B IC_{50} value gives prinomastat's "target" efficacious trough concentration of 40-50 nM. Significantly, the trough concentration produced by a 25 mg dose of prinomastat in cancer patients is 47 nM as denoted by the green bar in Figure 1.[3] This represents an "upper limit" of prinomastat exposure since this dose is associated with significant joint toxicity.

The same analysis applied to marimastat produces a similar conclusion. Mouse plasma protein binding was not determined for marimastat, however low binding was observed in rat and monkey plasma (~10%) and a 3-fold shift was observed in its gel A potency in the presence of 80% human plasma. Efficacy in the B16 model using minipump delivery occurred at a marimastat concentration of 167 nM. Based on several clinical trials the trough concentration produced by a 25 mg, bid dose of marimastat is approximately 400 nM.[20, 21] As with prinomastat, this value is not much higher than the trough concentration associated with efficacy in animal models. Interestingly, a recent publication indicates that a 25 mg dose of marimastat given twice daily produces the same survival benefit as gemcitabine in patients with unresectable pancreatic cancer.[11] While this dose produced musculoskeletal effects in nearly half the patients, *most of whom required dosing holidays*, it provides significant evidence of clinical response to MMP inhibition.

As mentioned above, no definitive accounts of preclinical efficacy have been reported for BMS 275291 and we have not characterized this compound in our labs (its structure was revealed as we were winding down our program). The intrinsic potency of BMS 275291 for inhibition of the gelatinases (mean gel A/B IC_{50} : 33 nM) is inferior to the hydroxamate-based compounds and its binding to human plasma was reported to be 46 - 77% (mean = 60%).[15] Without a trough concentration associated with preclinical efficacy BMS 275291 cannot be definitively compared to the other compounds in Figure 1. It is important to recognize, however, that at least one study indicates that trough concentration produced by BMS 275291 in cancer patients peaks at 430 nM (1,800 mg dose); a 2,400 mg dose was associated with a smaller C_{max} , AUC(24h) and C_{min} . [15] Independent of whether this trend is reproduced in other studies, it does suggest that there may be an upper limit to the exposure of BMS 275291 in humans and that it too may be an inappropriate tool to establish the clinical utility of MMP inhibitors.

ABT-518 is more extensively protein bound than the other compounds in Figure 1 and its affinity differs between mouse and human plasma. It is 94.4% protein bound in mouse plasma and 99.2% protein bound in human plasma which gives rise to a PBCed gel A/B IC_{50} value of 11 nM (mouse) and 80 nM (human). Efficacy in the B16 model was observed at a trough concentration of 260 nM, 23-fold higher than its mouse PBCed gel A/B IC_{50} value. Applying this factor to the human PBCed gel A/B IC_{50} value (80 nM) provides what is arguably an upper limit to the target trough concentration in humans (1,800 nM). Alternatively, using ABT-518's fold shift in gelatinase A potency in the presence of 80% human plasma (53-fold; presumably a more realistic, "functional" correction factor), yields a target trough concentration of 760 nM. These values are in the vicinity of the trough concentrations produced by the 50 mg dose of ABT-518 in cancer patients and would likely be exceeded by slightly higher doses assuming that its exposure continues to be linear with dose. *The inability of competitors' compounds to substantially exceed target trough concentrations could potentially be overcome by ABT-518 if higher doses are absence of adverse effects.*

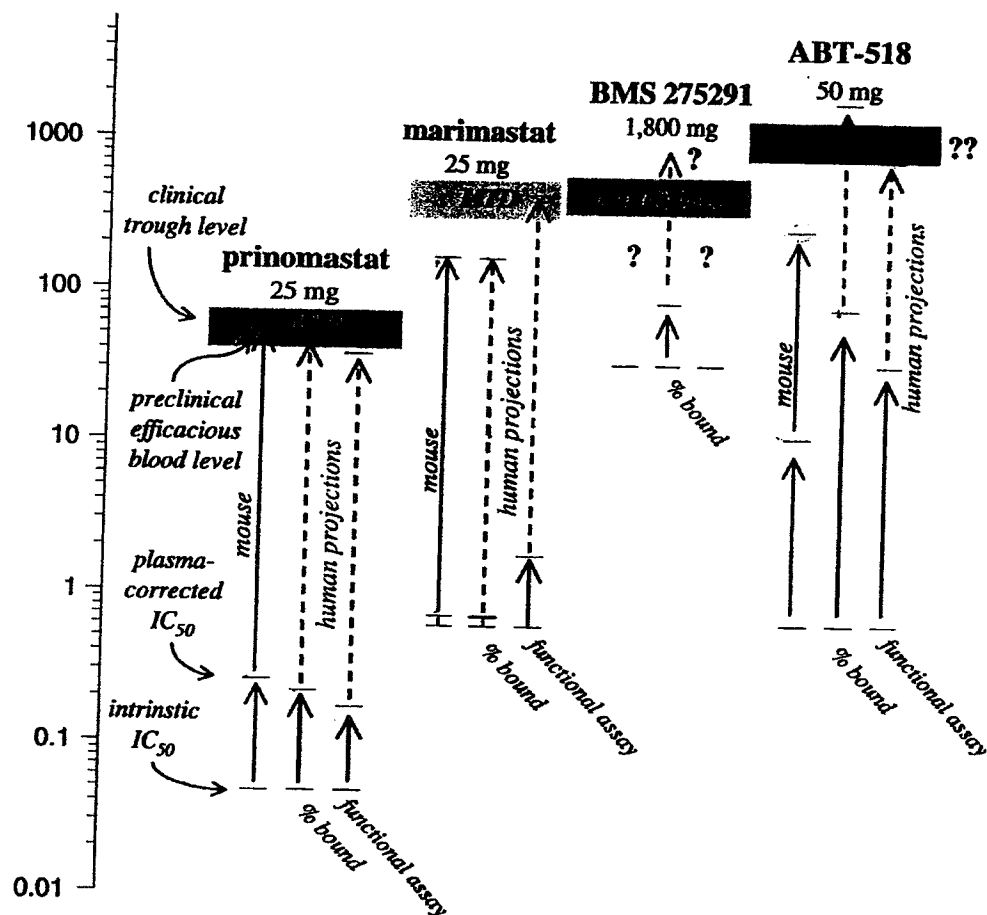
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Figure 1. Target versus clinical trough concentrations produced by prinomastat, marimastat, BMS 275291 and ABT-518.



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It is important to mention several caveats associated with the analysis presented above. For example, efficacy projections are based primarily upon data from a single model (B16 murine melanoma). Inhibitors were administered via minipump infusion in order to obtain steady state blood levels that were correlated with efficacy in the model. These steady state levels differ somewhat from the "trough levels" associated with efficacy generally reported in the literature, particularly in the case of prinomastat. Given the requirement for continuous exposure for maximal efficacy, we believe steady state levels provide a more realistic estimate of the required efficacious concentration than do trough levels, especially in the case of prinomastat where there is a large ratio between C_{max} and C_{min} after oral administration. There are also uncertainties about assessing the impact of plasma protein binding on efficacy as opposed to other factors such as tissue distribution. Given the relatively high affinity these inhibitors have for the target MMPs, the fraction bound in plasma may not accurately reflect the impact on activity. A functional assay of enzyme activity in the presence of plasma would seem to be a better approach and has been successfully pursued with human plasma; however, due to the presence of an unknown interfering substance, we have not been able to measure activity in mouse plasma. As mentioned above, we have no preclinical efficacy data for BMS. Rat and monkey plasma binding data were used in place of mouse and human for marimastat.

V. Path Forward

Based on the arguments raised above, the plan for further clinical studies with ABT-518 seems straightforward. First, the unresolved issues surrounding ABT-518's interrupted Phase I study need to be addressed. These include assessing the drug-relatedness of adverse events as well as the plasma concentration of the sulfonic acid metabolite. Second, it would be useful to have additional competitive intelligence on the clinical status of marimastat, prinomastat and BMS 275291, perhaps through Abbott's contacts with clinical oncologists familiar with the MMP inhibitors field. Most importantly, further Phase I studies should be undertaken to determine whether ABT-518 target plasma concentrations can be exceeded in the absence of dose-limiting toxicity. If target plasma concentrations cannot be achieved or if excessive metabolites are produced at these doses, development should be stopped. On the other hand, if ABT-518 crosses these hurdles, trials geared toward the assessment of efficacy should be initiated. It is important that Phase II studies include some measure of MMP activity so that evidence of functional MMP inhibition can be established prior to costly Phase III trials. *In situ* zymography detection of proteolytic activity in resected melanoma biopsies is one potential measure that could be used as a go/no go decision for ABT-518.[22] While conceptually appealing, validation of such a pharmacodynamic assay has not been achieved.

VI. Conclusion

To conclude, we feel that ABT-518 has the potential to be the first MMP inhibitor to demonstrate robust clinical efficacy. The points listed below provide a compelling argument as to why the development of ABT-518 should be continued.

- While the source of the MMPI-induced joint effects has not yet been resolved, the *in vitro* potency and selectivity of ABT-518 differentiates it from marimastat, prinomastat and BMS 275291.
- As a selective MMP inhibitor, ABT-518 exhibits efficacy in cancer animal models equivalent to competitors' compounds.
- Musculoskeletal toxicity limits the dose that can be examined by marimastat and prinomastat in cancer patients. Our analysis suggests that trough concentrations produced by these MMP inhibitors at their MTDs may be insufficient for clinical efficacy.

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- The encouraging human pharmacokinetic data produced by ABT-518, which avoids the large differences in C_{max} and C_{min} seen with competitors' compounds, suggests that trough concentrations substantially higher than its target levels may be achievable in the absence of limiting toxicity.

Please let me know if you would like to discuss these matters further.

VII. References:

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